IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 13-CV-4507(CCC)

IN RE: DEPOMED PATENT LITIGATION

TRANSCRIPT OF
PROCEEDINGS

(Public)

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Newark, New Jersey
March 11, 2016

B E F O R E:

THE HONORABLE CLAIRE C. CECCHI,
United States District Judge

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

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W I T N E S S E S

THE COURT: All right. We're going to begin. Let us, well let me just recap where are we at in terms of the exhibits? Do you want to finish the cross first or do you want to do the exhibits from yesterday because we did establish that we have a routine where we go through the exhibits the next morning.

MR. ALY: We did, your Honor. Mr. Sitzman sent an e-mail last night. I think we agree and all the defendants seem to agree we would like to refer to the transcript to enter some exhibits.

The transcript, because of the lengthy day yesterday of course is not yet complete. I completely understand. So we'd like to use the Thursday and Friday transcripts and do that on Monday morning.

THE COURT: That sounds like we are all in agreement on that.

ATTORNEYS: Yes.

THE COURT: All right. That's fine. So let's proceed with doing cross.

MR. ALY: We will have the witness return to the stand.

THE COURT: Dr. Gruss, good morning. How are you?

THE WITNESS: Good morning. Fine, thank you.

THE COURT: I remind you that you remain sworn.

Let's continue the cross.

MR. GLANDORF: Just a few things we wanted to discuss on the exhibits. Again, we have the translation issues with in fact the same two documents that we had yesterday. They are defendants Exhibits 1060 and defendant's Exhibit 1332.

I know with regard to 1060 that the defendants also put our translation into its binder. So thank you for that. As far as defendants Exhibit 1332, we have our translation here and we would like that to be provided to him. We can do it now or if it comes up.

MR. ALY: Now is fine, your Honor.

THE COURT: There's no issue with that, right?

MR. ALY: No issue.

THE COURT: Okay. That's fine on both of those exhibits then.

MR. GLANDORF: We also have a translation, your Honor, that we don't believe we have ever seen where it's newly produced. We want to note that that's defendant's Exhibit 986.

THE COURT: Okay. Aside from it being a new translation, have you had an opportunity to look at it or not really?

MR. GLANDORF: We had not had a chance to evaluate it so we would reserve that right.

THE COURT: That's fine.

MR. GLANDORF: And then finally, defendant's Exhibit 1097, that's an exhibit we have a foundation objection to an exhibit that was explored at his deposition. And it was clear at his deposition that no foundation was established. So we ask that that will be excluded as well.

THE COURT: You know what, again since it is a bench trial, let me see how it goes. I think we can explore it. Counsel can ask the appropriate questions with respect to the exhibit and then I will treat it accordingly and give it the appropriate weight.

MR. ALY: Thank you, your Honor.

MR. GLANDORF: May I approach with this translation?

THE COURT: Yes. Please do. Good morning.

MR. ALY: Good morning.

THE COURT: Thank you, your Honor.

M I C H A E L G R U S S, previously sworn, resumes.

CROSS EXAMINATION BY MR. ALY:

Q. Dr. Gruss, good morning to you as well. Thank you for your time here this morning.

First I just want to find out about the area in which you work. You work on the analytical side looking at molecules from an analytical side, is that correct.

A. At what point in time do you mean?

Q. Let me distinguish it. You don't synthesize the

molecules, you do tests on molecules after somebody else makes them. Is that correct?

A. You mean today or.

Q. At Grunenthal.

A. At Grunenthal when I started.

Q. At Grunenthal, at anytime that you worked there, you were not the one making the compounds. You were the ones testing the compounds, correct?

A. I was not doing the organic synthesis. I am not an organic chemist. I am an inorganic chemist by training. So what we did, we did crystallization studies it my laboratory. I did not run the analytical laboratory. But I forwarded samples or my staff forwarded samples for crystallization and analytics.

I had a look at the samples. I install the workflows, how maybe samples are produced for crystallize and then transfer to the analytical department. I myself also yeah used the means by interpreting the results from the analytical department.

Q. And when you got to Grunenthal, you were not asked to make new organic compounds, correct?

A. Not, no.

Q. When you got.

A. That's correct. Sorry.

Q. When you got to Grunenthal, you were asked to gather

information regarding crystal data about Tapentadol. Is that right?

A. Not just crystal data. So when I joined Grunenthal as I stated earlier I was hired --

Q. Among other things -- let me rephrase. I am sorry to interrupt. I want to rephrase to make it cleaner because you might be explaining quite a bit.

What I am most interested in is the job that you had when you started at Grunenthal was to gather information about the tests that had to be done. Is that how you started?

A. Not only that. They asked me to do additional tests on samples that are been produced. So I gathered information and collected information and I look at that and also started to gather new information on samples that already existed. And also for samples that were being produced.

Q. Dr. Gruss, did you see any XRD data, the crystal data that is batch 0 that had already been done before you arrived at Grunenthal?

A. I think we stated that clearly yesterday the sample has been produced in 1994 and we forwarded it a sample for x-ray analytics to the university of Aachen in 2001 time frame.

Q. The year you arrived at Grunenthal was not -- was after 1994, right?

A. I joined Grunenthal in May 2000.

Q. And in 2000 when you joined Grunenthal there was no

x-ray data or XRD data for batch one that had been prepared, correct?

A. I don't know which batch, what batch one is. Do you have some data for batch one?

Q. Fine. So, that's what I want to make sure. Do you know anything about something people have called batch one at Grunenthal from an x-ray crystal data point of view?

A. Sorry, sir, you're talking now about batch one. So I don't know how many batches have been produced from BN 200. I know about batch 0. And I later seen other batch data. But at that point I don't know of batch one.

Q. As of today now we are in trial do you have any x-ray data that shows the crystal information about batch one of Tapentadol hydrochloride?

A. What is batch one?

Q. Fine. You don't know anything about batch one or whether even a batch one Tapentadol exists. Is that true?

A. So the first sample, so the enumeration at Grunenthal started with 0. So the first batch was batch 0 to my knowledge. So that's also general enumerations keep at Grunenthal. They started with 0 and then continued with later batches.

If it might have been the batch one, I don't know. Might have already been consumed batch two but batch whatever. As far as I remember, I seen something like batch nine or so

but I can't tell you what data I saw about that.

Q. I'm sorry, I don't think I heard an answer to my question.

Sir, do you know, as of today, whether there's any x-ray crystal data that Grunenthal has made regarding batch one of Tapentadol?

A. Not to my knowledge.

Q. Now, you showed us a demonstrative yesterday with the timeline. I'd like to talk about that with you. That's demonstrative Number 1.

This is a timeline you spoke with us about. Is that right?

A. Yes.

Q. And on the top left you have batch Number 0 synthesized and that was in 1994, correct?

A. Correct.

Q. And when you arrived that was in 2000, correct?

A. Correct.

Q. Now, you referred yesterday to Miss Lischke's testing and analysis that she had done in 1998, correct?

A. Correct.

Q. Now Miss Lischke's testing was DSC, it was not XRD, correct?

A. To my knowledge, she did some analytical studies.

Q. And DSC that you put on the demonstrative, that's heat

testing to see what forms of Tapentadol may exist as you raise the temperature. Is that right?

A. Sorry, I did not put data from this list on the demonstrative. What do you mean? Maybe I did not get question.

Q. I'm asking DSC, you understand, is the test where you put the crystal or put a solid in a machine and you raise the temperature to see what happens to that overtime?

A. You put the sample in the DSC and you raise the temperature and you can lower the temperature as well in that machine and you see what effects happen with that sample.

Q. That's a different test than the xray diffraction test, the XRD, correct?

A. As I explained yesterday, you apply several techniques to investigate and fully understand our system.

Q. And the one claimed in the patent your '364 patent that's the only x-ray claims, correct?

A. I have to take look through it. I am for sure that we -- so there are figures given with respect to x-ray data and also with respect to spectroscopical data.

Q. In x-ray data, this is the graphs you looked at yesterday. We will look at one. But for now I just want to make sure where the x-ray data comes from.

You put some samples in a machine and it spins an x-ray beam around that sample, correct?

A. There are different analytical machines, x-ray machines. I don't know exactly the beam spins. As far as I know the beam is fixed and raised on the sample. We spoke about capillaries, there are different geometries. And yeah, I don't know exactly what the set up was, how the sample has been determined.

So if you say spinning around, that must not necessarily be correct.

Q. But the x-ray machine does take angle measurements. Either the x-ray that moves or the sample parts that move around that are angles that go around the sample and beams that are directed at the sample, right?

A. So, what is determined in the diffractogram is the diffraction angle.

Q. And the diffraction angle is an angle based on putting an x-ray to the sample and to see how that diffracts?

A. So, I am not an expert really with the set up of the machine. So I think I started to explain here how the diffraction actually works. I need to have some slides to illustrate it.

Q. But, the point that I'm making is it's a machine that you put the sample in a machine and a result comes out, correct?

A. For the x-ray powder pattern is measured on the sample, put on the machine and the machine, as I explained yesterday,

raised x-ray rays on it then the diffraction pattern is recorded and then yeah, start to --

Q. Dr. Gruss, when you arrived in 2000, did you see the 1989 report that Grunenthal had on hand? Did you see any 1989 report?

A. As far as I remember there has been data put together that also put together Miss Lischke's data, yes.

Q. All right. Let's look at that exhibit, plaintiff's Exhibit 387.

A. Is it in my binder here?

Q. It should be in one of the two. I apologize there are two binders here.

A. No, this is Buschmann. I don't know, I don't want to look at the wrong binders.

And the number please again.

Q. Plaintiff's Exhibit 387.

A. First I have demonstratives then there is PTX 0491 I suppose it should be before.

Q. It should be in order.

THE COURT: You know what, I think he only has one notebook.

MR. ALY: Just a moment. May I approach your Honor?

THE COURT: Yes.

Q. And it's on the screen as well.

A. I prefer to put it up here.

Q. That's why we have the binder. I'm glad you are making good use.

A. Thank you. DTX 311 then it comes DTX 910.

THE COURT: Volume two.

THE WITNESS: Do you know?

THE COURT: Volume two towards the back.

THE WITNESS: My binder starts with 1056. So this starts with 1056. This starts with, it's not enumerated. I apologize.

THE COURT: It's okay.

Q. Because this will happen a few times, let me explain what you are seeing in the binder since you are using the binder.

The first volume starts with DTX, D as in delta. And then it is in number order from there. But then after the D runs out, it starts P, P as in Peter and then those numbers go from there.

THE COURT: Hold on 1 second. Okay go ahead.

MR. ALY: Thank you, Judge.

Q. Had you seen this report, this is DTX 387 when you first joined Grunenthal?

A. As far as I remember I might have seen it, yes. It might have been amongst the data, the information I collected.

Q. The report is that of the crystal structure of compound

CG 0053, correct?

A. That's correct.

Q. That compound refers to Tapentadol. You explained that yesterday, correct?

A. That's from a date 1998. I don't think, 6th of April or 4th of June. I'm not certain. Maybe 4th of June. CG 550 is temperature for Tapentadol hydrochloride.

Q. If you can focus on Page 3 of the document which has Experimental on the top. Isn't the document confirming that as of 1998 Grunenthal had all of the unit cell information to show that form A or monoclinic form of Tapentadol had been developed?

A. So that, no, no.

Q. Dr. Gruss, can I point your attention to the paragraph that describes the cell constants and orientation matrix. There is data provided here for the cell parameters of unit cells of the crystals that were seen there, correct?

A. There are the unit cells of crystals of the form determined here. But, at that point in time there was just limited information that was available. So this was just a snapshot on the crystal structure on the form we afterwards called form A.

Q. And already at that time that it was explained that's the monoclinic shape, correct?

A. The monoclinic properties, but that does not tell you

that there are not other cells already existing.

Q. You also said that you had hired SSCI in 2001, correct?

A. I said that Grunenthal has hired SSCI. So there was --

Q. Sorry. At the time you were at Grunenthal in 2001, Grunenthal hired SSCI, correct?

A. To study a systematic polymorphism, to perform systematic polymorphism studies. That was intention which Grunenthal has hired SSCI.

Q. Let's look at DTX 1279 and --

A. DTX 12?

Q. 79.

A. Yeah. Okay.

Q. And by August 2001 in the middle you had received an e-mail referring to the SSCI project update report, correct?

A. I can't remember that. So, this is an e-mail. So 1279, that's an e-mail sent from Sattleger, Michael sent to Fischer, Dr. Andreas.

Q. If you look at the middle it's got your name in the middle as the recipient of that e-mail August of 2001, correct?

A. You mean below.

Q. I'm pointing to it with the laser on the screen. You can look at it there as well.

That's your name right?

A. Yeah, that's my name.

Q. And Dr. Gruss, let's turn to the next page. It's Page 1 of the SSCI report that is dated August 15, 2001.

That also again has your name as the representative?

A. One second. I'm still looking at the other exhibit what is there.

Q. Dr. Gruss, if there's information that's needed to answer the questions, your counsel can have you look at them on the redirect. But for right now I'm just walking through the documents to make sure we agree on what's there.

A. I apologize if I am not so familiar with the proceedings here. I apologize.

Q. Let's look at this page here. We got your name is appearing here on Page 1 of the contact report, correct? Sir?

A. Yes.

Q. Thank you. Let's turn to the next page the update report on the first paragraph of the SSCI report from 2001 explained to you that when CG 5503 lot CEHS 98-99 was received, it was immediately analyzed using XRPD. Do you see that?

A. Yes.

Q. And SSCI reported to you that the XRPD pattern obtained from this sample was designated as form A and shown in Figure 1, correct?

A. The sample has been shipped from Germany to SSCI so that's across the ocean. And then it has been investigated at

SSCI.

Q. Are you suggesting, sir, that something happened to the sample from the time it was shipped to Germany to the time it was arrived in Indiana that would effect this test?

A. That's possible.

Q. So, did you rely, as a company, on the results of this test to explain what form you obtained?

A. What I explained yesterday, so the x-ray analytics at SSCI --

Q. Did you rely on this?

A. The x-ray analytics SSCI did was a snapshot in the time when they received the sample. And when they did the investigation of the sample that they had received, that must not necessarily be the same as it might have been in Germany or, you know, that's a sample drawn and handled in uncontrolled conditions.

Q. That's not my question. My question, sir, is did you rely on this document for information about the polymorphic form of Tapentadol hydrochloride?

A. The document tells me that that at that point in time when they did the x-ray part of the diffraction data, they determined they called it form A.

Q. You're still not answering my question.

Did Grunenthal rely on this data that it received from SSCI?

A. So, that was a snapshot in time. And we took that data and considered it was in our further, yeah, considerations so that to put all information together that we had.

Q. So you relied on it as part of the information. Is that correct?

A. At that point in time I think so.

Q. Now then if you look at the third paragraph of this exhibit, the paragraph says that there was a characterization of form A that was completed, followed by a polymorph screen. Do you see that?

A. So again please your question. Sorry.

Q. The question is, there was a characterization of form A and then a polymorph screen was performed. Do you see that?

A. Yes.

Q. And in fact the idea for SSCI, their project was to try to produce as many new forms of Tapentadol as possible, correct? That was their task?

A. So, as I mentioned yesterday, we knew already about two forms when we forwarded and when we hired SSCI. And so our idea was to get as much information as possible about existing or new forms of Tapentadol. That's the intention of the polymorph screen.

MR. ALY: Your Honor, I would like your Honor, if possible, to instruct the witness to please answer the question to the best of his ability yes or no. If there is more

explanation that would be redirect.

THE COURT: Why don't you rephrase the question? Ask it again and then let's get a response.

Q. Was the job that you assigned to SSCI to produce as many new forms of Tapentadol as possible?

A. The job was even more, so the answer is more.

Q. So when they say, SSCI says to you that their job is to what, produce as many new forms of CG 0053 as possible, you are saying they weren't doing what you asked them to do? Is that right?

A. That is part of their job. So, it was also characterizing the existing forms and to find new forms, as I stated yesterday, new forms, new polymorphs to understand better the system.

Q. And in terms of results, SSCI in 2001 told Grunenthal that there were only two forms, A and B, correct?

A. We knew already before SSCI told us that there are two forms.

Q. So, SSCI confirmed that there are only two forms of Tapentadol, correct?

A. As far as I remember, SSCI did not reveal any new forms that have not been known to us at that point in time.

Q. Right. And then to find out what the behaviors are from A and B, they found, SSCI reported -- I'm reading from the document now the fourth sentence of that paragraph, that During

this investigation, we discovered that upon heating form A to 75 degrees celsius, it converts to a new form, which was then designated as form B.

Do you see that?

A. I see that.

Q. So, form A you knew was a room temperature stable polymorphic form of Tapentadol, correct?

A. Form A at room temperature thermodynamic stable modification.

Q. And when you take that form A and you heat it up to some temperatures here, they used 75 degrees celsius, then it became form B.

Is that right?

A. No. The temperature range here is not correct, as I stated yesterday that we, Dr. Lischke had an already recorded the data. And when I understood the data, I attributed events of the DSC to about 40 to 50 degrees as being the, yeah, the temperature range where one form converts to the other form.

Q. Let's continue reading that towards the end. Total conversion from form A to form B was complete by 50 degrees celsius.

Do you see that? That's consistent with what you just said. Do you see that?

A. This relies on one experiment of variable temperatures.

Q. What we see here at room temperature, if you make

Tapentadol, you get form A. And if you cook it to 50 degrees C, that's when the SSCI forms B?

A. That's not correct.

Q. At form 50 C it's also correct that the total conversion happened from A to B but then if you let it cool back, the form B returns to form A. Didn't they report that to you?

A. That's not stated here. So, the point is you have to consider every single experiment and they had just a snapshot.

Q. You've answered my question, sir. You said that it wasn't stated. Let's read that together.

Doesn't the SSCI report also say that variable temperature XRPD had been done showing that upon cooling form B to room temperature, form B converts back to form A?

A. That might have been in this particular experiment.

Q. And also in the SSCI experiments, if we look at the next paragraph, the goal then turned to see if form B is only happening in these unusual circumstances, how can we make a stable pure form. That was their goal, right?

A. No, sorry, I'm not really familiar with that so I have to read it in answer to your question.

Q. Let's read it together.

A. So there have been many experiments and that what you are presenting to me now is just a snapshot of a bunch of experiments that they did, right.

Q. Sir, if I take anything out of context, your lawyer will surely ask you a number of follow up questions.

Right now I want to work with, I agree it's one report. I agree it's from SSCI. Now let's read the report. It says the goal SSCI had --

THE COURT: Why don't you do this, do you want time to read it?

THE WITNESS: Of course.

THE COURT: Let him read it. Take a few minutes to read it and when you're done then ask your questions.

MR. SCHULER: Your Honor, Roxane would ask that this time be allocated to the plaintiffs.

THE COURT: He will be done in a minute.

THE WITNESS: Okay. So, I roughly read through it so please --

Q. Thank you. Dr. Gruss, actually at this point since there's several other documents I will be going through, I was just curious to know is this Exhibit one that you had reviewed as we're gearing up for the trial?

A. I can't remember looking at that recently.

Q. And this document is not one you had used on the direct examination yesterday, correct?

A. As far as I remember, as I mentioned, I haven't recently looked at it and it just represents a snapshot of time, the knowledge of SSCI at that point in time.

Q. And SSCI was writing in 2001 that the goal of their project turned to the production of stable form B, correct?

A. A part of the characterization was to understand the relationship. And later on I think it was clear that at room temperature form A is thermodynamically stable and a form B is a metastable form. But it doesn't necessarily mean it's unstable at room temperature.

Q. The goal of the project that SSCI did -- do you see that they report that it turned to the production of stable form B?

A. The goal, as I mentioned, was doing the polymorphism study in order to characterize the system.

Q. And then when they were looking for form B, one of the attempts they did involved heating in a TGA at elevated temperatures. Do you see that?

A. I see that.

Q. They report, SSCI does, show still form A was produced, correct?

A. But there is nothing said about a temperature range where they operated. There are no details given about the conditions. And as I mentioned yesterday, the space for polymorphism is nearly like big as universe.

So, depending on what type of experiment you do, you get different experiments led to different results.

Q. Actually so they do report the results, don't they?

A. Sorry.
Q. Let's look at Page 8.
A. Page 8.
Q. Table seven. Next page of the document. It's Page 8 of the report.
A. Page 7.
Q. This is it. It's called Heating Studies, right?
A. Yes.
Q. And they told you the conditions. They take the form A, they heat it to 75 degrees celsius for five minutes, right?
A. That's said there.
Q. And they got form A as their result, correct?
A. But there's, let me see what the A means. Okay. That's what I stated, that was the impression at that point in time.
Q. And let's look at what it took to get form B. It took starting with the mixture of form B and A and then heating that for 125 degrees celsius for 30 minutes.
Do you see that?
A. I see that.
Q. And that resulted in form B when they did it that way, correct?
A. As I stated earlier, different experiments can lead to different results.
Q. Let's go back to the page we were looking at which is

Page 3 or Page 2 of the report, the bottom paragraph.

You mentioned that form B was metastable. So what they did at SSCI in 2000 was attempt to isolate the metastable form B now by dissolving form A in various solvents followed by centrifuging under vacuum.

Do you see that?

A. That is one time the experiment they have conducted.

Q. That still had form A as a result, though, and mixtures of form A and B, correct?

A. These type of experiments seems to have led to a production of a mixture of A and B.

Q. Now, they took a sample in form A and milled it for longer than 15 minutes. And that still only resulted in, at best, a mixture of form A and B. Is that correct?

A. Yeah. But it's also stated that it milled at different temperatures.

Q. There were two different tests that were done. One there was a mixture of form A and B that was milled for longer than 15 minutes. That resulted in the mixture of form A and B, correct?

A. It says here a mixture A and B was formed when the sample is milled longer than 15 minutes. A study looked at table 9. We haven't yet looked at table 9.

Q. I'm reading through what the SSCI reported. The SSCI then reported that form A was milled at subambient temperatures

in a cryo miller and then milled while submerged in liquid nitrogen. Do you see that?

A. I see that.

Q. And after several cycles of doing that they only still got, at best, a mixture of A and B, correct?

A. That seems to be the result of the experiment at that point in time.

Q. And then SSCI took a hydraulic press at 5000 P.S.I. for several days to form A, correct?

A. I see that.

Q. Form A didn't even convert at all in that condition to form B, true?

A. And that's why form A is really good.

Q. And the conclusion SSCI -- hold on. Sorry. You said?

A. So, form A did not convert under pressure and that's good.

Q. And form A is good because it's stable, correct?

A. Form A is stable and thermodynamically stable at ambient conditions.

Q. SSCI reported in 2001 to date the only repeatable method for making stable form B involves milling form A for at least 15 minutes to get a sample that is a mixture of form A and B, correct?

A. So the document is dated 2001, 15 August. So as we showed yesterday, the polymorphism study was still ongoing at

the time. It was just a snapshot of their knowledge at that point in time. So as I stated to date.

Q. Then to make it stable then they still had to heat it after they did this milling to 125 degrees celsius, correct?

A. That was I think their understanding and the result of their, of that type of experiment at that point in time.

Q. Now, has Grunenthal at any point manufactured Tapentadol by milling the Tapentadol and then heating it to 125 degrees?

A. I don't know what Grunenthal did at any point in time. So I know for sure that there have been samples of form B produced at Grunenthal.

Q. I'm asking a different question.

A. What do you mean manufacture the synthesis or what you mean.

Q. Very good point. Let's talk specifically to making Nucynta.

Did Grunenthal ever make Tapentadol by milling Tapentadol and then heating it to 125 degrees celsius?

A. Sorry, I do not understand the question. To make Tapentadol, to mill Tapentadol so --

Q. Let me try again.

A. I have not understood it, sorry.

Q. Sorry. When making Nucynta, the Tapentadol that goes into Nucynta, did Grunenthal ever mill the Tapentadol and then

heat it to 125 degrees?

A. I was not responsible for the formulation, for the preparation of the tabletting materials. So I can't tell you what Grunenthal ever did. And even not, when at what point in time do you mean? So I was in the process development department.

Q. Do you know if Janssen, the company that later sold Nucynta, had sold product where they made the Tapentadol by milling it and then heating it to 125?

A. I don't know what Janssen did at any point in time.

Q. You also mentioned yesterday, sir, you retained, through Grunenthal, Crystallics, another lab that --

A. We did what?

Q. Hired Crystallics?

A. So Grunenthal hired Crystallics in order to investigate the system of Tapentadol hydrochloride crystallization in more detail.

Q. Let's look at plaintiff's Exhibit 379.

A. So that's P?

Q. PTX 379.

A. I think I misunderstood the nomenclature. I'm at 379.

Q. The first page here has the top header with the Crystallics final report dated May 2003.

Do you see that?

A. I think that report stated the knowledge of Crystallics

at that point in time.

Q. And Crystallics had written this memo to you, correct?

A. Yes, I was contacted. My name is stated there.

Q. And the reason I was asking about the SSCI report is, and whether you had read it, is because yesterday on your timeline, if you can look at Exhibit 1, you had referred to hiring SSCI to do some work.

Isn't that right? The demonstrative.

A. So, you mean why we please, I did not get the question, why SSCI and Crystallics you mean.

Q. Let me just --

A. Different companies.

Q. I understand that. Right now I'm just saying for April 2001, when you were talking about this yesterday on your direct examination, you were explaining to us that you hired SSCI to do work on Tapentadol, right?

A. So, as I mentioned yesterday, Grunenthal decided, that was a joint team decision to hire SSCI. And as I stated also yesterday there have been just a few companies on the market and we decided to go with SSCI at that point in time because from all perspectives that seemed to be the appropriate company to do the type of studies we needed at that point in time.

Q. I'm asking you yesterday you didn't show us results of SSCI, did you? You just showed us that they were hired to do some work?

A. I think my counsel presented data.
Q. And for Crystallics you also mentioned in this timeline you put up that Grunenthal had commissioned Crystallics to investigate Tapentadol Hydrochloride, correct?
A. That's correct.
Q. Is that a report that you reviewed to prepare for trial?
A. I can't remember.
Q. Let's look at, that's where the plaintiffs 379 that was on the screen. And in the introduction, let's highlight the introduction. There is a reference that an accelerated experimental program with 97 experiments has been performed at Crystallics, correct?
A. That is stated there but 97 experiments is not so much.
Q. And so 97 experiments in your field, even that number is not very many experiments?
A. It just gives you also just a snapshot of that type of things being investigated.
Q. And so the person doing that day-to-day work routine lab, they say here is 97 experiments for you, you would say that's not very many?
A. That's a snapshot, yes. That's a part of the work that was spent over many years. So a lot of experiments has been performed.
Q. And what they were reporting is that two polymorphic

forms have been identified to date, form A and form B, correct?

A. At that point in time in 2003 that's their statement.

Q. And let's look at the next page for Crystallics on the side that says the product section.

When Crystallics said here's what we got from Grunenthal, they reported, did they not, that form A had been delivered as a white powder?

A. That refers to the batch they stated.

Q. And the form B that Crystallics received was reported as an off white powder, correct?

A. That says there.

Q. And you know, sir, that the reason for the difference is because of impurities that are in between A and B, correct?

A. No.

Q. Let's look at Page 10 of this report. The effect of impurities is the analysis that Crystallics sent to you and said that Grunenthal --

A. Hold on. I'm not there yet.

Q. By all means, sir.

A. Sorry.

Q. On the top line, Crystallics says that Grunenthal had previously indicated that the polymorphic form of Tapentadol is affected by the amount of the impurities, two are given in the mixture upon crystallization.

Do you see that?

A. So that might have been our understanding at that point in time. As I stated earlier, that was just a snapshot in time. That might have been the understanding at that point in time. But, as far as I remember the outcome was the investigations was that there was no impact of impurities.

Q. Let's look at the next paragraph after this one is here. Crystallics in the All experiments section says, second sentence, higher amounts of one of the impurities was observed to have a larger influence of forms of polymorph B and other impurities, correct?

A. So let's state it, they have compared, as far as I understand it, the different impact of the different impurities but that does not show, as far as I know, the conclusion has not been really an effect of the impurities as such on the outcome.

Q. So, I'm just --

A. As far as I remember.

Q. What Crystallics reported to Grunenthal in 2003 is that when you have these certain impurities, they have influences on the formation of polymorph B rather than A, correct?

A. This sentence says that the one impurity named GRT 0912Y was observed to as the larger influence on the formation than the other. But that does not reveal, yeah.

Q. All right. Let's go back to the timeline that you put yesterday, demonstrative one, Gruss demonstrative one.

Now I want to shift over from the reports that you received to talk about the batches that were tested that you talked about yesterday. The batches that you talked about yesterday were three, batch Number 0, and then two Mueller tests. Is that right?

A. So we talked about several of the batches. I think there has also been other batches mentioned.

Q. That's on the timeline for batch Number 0. That was what you said was synthesized in 1994?

A. That is my understanding, yes.

Q. You were not at the company in 1994?

A. Correct. No.

Q. And in 1994 when batch 0 was made, you don't know how it was made, correct?

A. In 1994 I did not know that. I did not even know about Grunenthal. And I was at my studies at university of Giessen. But later on what do you mean if I then know how it was produced? So I am not an organic chemist so.

Q. Well, my specific was question in batch number 0 you don't know how it was made, right?

A. I am not there at that point in time in 1994.

Q. Let's fast forward now to 2001. You reported in your timeline that XRPD, this is an x-ray powder diffraction analysis, revealed that batch Number 0 is form B, correct?

A. I sent out a sample, a batch 0, the x-ray powder

diffraction and results I received is form B.

Q. To the best of your knowledge, that's the first time batch 0 was ever tested for x-ray diffraction was 2001? Is that right?

A. To my knowledge that was the first time that batch 0 has been tested with respect to x-ray powder diffraction but --

Q. You see on the timeline there's a gap between 1994 and 2001, obviously about seven years, correct?

A. I see that. And that was why we was so amazed because it indicated to us that form A is a new form and Form B has already been stable sitting there for 7 or 8 years.

Q. And when we are looking at this batch Number 0 and the time between '94 and 2001, in between it's that 2001, 2002 time frame in between there, where did you get the sample from to do your test? Where did you pick it up from physically?

A. I can't remember.

Q. Who handed this to you, this form 0 sample?

A. I can't remember.

Q. What form was it, vial, a box, a crate?

A. As far as I recall, it was a vial and usually vials were stored on a shelf.

Q. What color was the material?

A. I can't remember.

Q. Who was the person that had kept it from 1994 to 2001?

A. I can't, I don't know. It can be many. But, usually

samples are stored on the, yeah, how do I say, on the shelf or I don't know what the state of the sample was.

Q. What was the storage conditions over those seven years?

A. I don't know but it's very unusual to store samples in the oven for that period of time.

Q. Was that material -- how much material was in that vial that you saw?

A. I think we went through that yesterday that the person that did the experiments said that it was just a tiny amount of material.

Q. What do you mean by a tiny amount? Was it less than a hundred milligrams?

A. I don't know how much it was.

Q. Are there any documents showing that the same batch that was made in 1994 was really the same batch tested in 2001, sir?

A. As far as I remember that sample that I received was coded batch 0.

Q. So, the only indication that you have is receiving a sample that says batch 0. That's what you saw?

A. No, we have other indications because resynthesis, we did the resynthesis in order to make really sure that we are not lying.

Q. Trust me I will talk about that.

The resynthesis you are talking about to be the Miss

Mueller work, correct?

A. Yes.

Q. Right now I'm talking about batch 0. There's no documents that you showed us to say at that time material that was created in 1994 was really the same material that was tested in 2001. You didn't show us any documents to that?

A. What I said was we had documents that stated sending out batch 0 sir and that we received the results and reports with respect to batch 0.

Q. And batch 0, did you at anytime look at the lab notebook for the method in which batch 0 was created?

A. I think I have seen that.

Q. Let's look at DTX 974.

A. Do you have the binder?

Q. DTX 974 I am informed actally was inserted later and it's therefore it's going to be in one of the covers, Dr. Gruss, for volume one. And volume one, if you look inside the front cover --

A. Okay.

Q. You can look at the --

A. Let me put it so we have everything.

Q. Smart idea. And this DTX 974 is the English translation of the lab notebook regarding batch 0 correct?

A. Is the original also there?

Q. The original would also be there in other material. We

can pull it up for you if you want to see it.

A. Please, please I would like to see the original.

Q. Okay. Let me see if it would make a difference for the one question. If it does, we are pulling it up in a moment.

A. Please hand me over the German version. Please give me the German version.

Q. May I ask you the question first so you can tell me if you know a fact? I just want to know if you know one fact about -- you can refer to it. If it does help you, that's fine.

But my question to you is do you know if the batch 0 that was reported had a melting point or not?

A. Please give me the German version.

Q. Thank you. We will. I'm told we will get back to you to have that on your screen and you will be able to take a look at it momentarily.

In the meantime I want to talk to you about exhibit PTX 1547.

A. PTX 1547. I have 1513 and I have --

Q. It's in the plaintiff's binder. I apologize because it was one that you had used yesterday.

A. Sorry.

Q. It's my fault.

A. I just need to find it.

Q. It's my fault. I thought yesterday we were looking at

it on the screen but it's helpful to look at it in front of you as well.

A. Okay. I'm sorry.

Q. Thank you. And Dr. Gruss, what you were explaining to us yesterday was when we have these peaks, there's blue signals with peaks and red signals with peaks, correct?

A. What I explained yesterday that we see two different powder, that we see two powder diffraction patterns.

Q. And the blue one is the one that you had measured that you were testifying was the batch 0?

A. No. I have testified that I sent that sample out and that I received the result. I have not tested that with respect to putting on the x-ray machine. But I've compared it in order to investigate which form was in it.

Q. Thank you. And the red one is a standard called CEPM-1 MA, correct?

A. No. The red one is a sample or a pattern that we used at that point in time as a reference to compare.

Q. We you say reference --

A. No, it's not reference standard. It's different. It's a reference pattern. So it's a pattern that I used or we used in order to quickly compare the form. And what I stated yesterday that I could not see form A in the BN 200 batch 0 sample.

Q. That's what I wanted to find out. When you did this

test or you asked for this test to be done, did you send it to the lab, both the standard, both the reference CEPM 1A and the batch 0 or did you just send them the batch 0 sample?

A. I sent various samples to that laboratory. And with respect to x-ray powder diffraction data, it's not like any other method necessary to run the standard simultaneously with that.

Q. I'm only asking you whether you sent both of the things pictured here as samples to the lab or not.

A. I know that I sent sample BN 200 batch 0. But, I don't know when or to whom I sent the sample of CEPM 1A for testing.

Q. And yesterday you were able to look at this just naked eye and say I don't see any form A here. Is that right?

A. I don't see any form A in batch BN200 batch 0. That is what I said yesterday.

Q. Can you give us some examples of peaks that we can talk about that you know to be associated with Form A that are not here?

A. So sorry. Please repeat the question.

Q. Sure. Can you give us examples of peaks that you know to be associated with form A so that we can both look and agree whether they are here or not?

A. So the peaks for form A are listed in the patent for example and I did that comparison at that point in time. And I did it recently.

Q. But sir yesterday you were able to look at it and say I don't see any form A. I'm wondering what analysis you did yesterday or did you do some analysis yesterday on the stand?

A. I quickly compared that and yeah.

Q. But you didn't actually tell us about any peak numbers to look at to see whether A was there or B was there, did you?

A. I just said yes that BN 200 batch 0 that I don't see any peaks of A there.

Q. That's the issue I wanted to ask you about with respect to this exhibit and that's the blue lines here are the ones, and I'm shaking on purpose to refer to the fact that there's a lot of ups and downs, if you will, as the thick line goes across the screen.

And the question to you is do you agree with me that there's noise in the blue signal?

A. I think there is noise in every signal. The importance is the signal to noise ratio that's okay with me.

Q. So when you are talking about the signal to noise ratio when we see the blue, there's a lot more vertical up and down for, you know, within each one or two steps as compared to the red line, for example, correct?

A. So I don't know what you are referring to with the up and downs.

Q. I see. Let's talk about the thickness at 10.0 for example the thickness of the 10.0, the blue line, it's thicker

than the red line at 10.0.

Do you agree with me on that?

A. I don't see what -- I think that can. I don't see that it's ten now. Maybe. Okay. Thank you. It seems to be more noise there, yes.

Q. When we were talking about peaks yesterday, you testified that the size of the peak, the height of it doesn't matter, correct?

A. So most important is the position of the peaks because the height of a peak can be affected by yeah the preparation of the sample and the types of crystals.

Q. Precisely. As you say, there is a signal to noise ratio. There's a detection that's built into a test like this?

A. I don't know the limit of detection.

Q. Do you agree there is a limit of detection?

A. Generally in every analytical method there is a limit of detection as far as I understand.

Q. Do you know what the limit of detection was for this particular equipment, for this particular test that you talked to us about yesterday?

A. No, but it was the testing method that we had at that point in time available for our needs.

Q. The limit of detection, you will agree, is the limit below which there could be other samples, but the x-ray pattern won't show that?

A. What I said is we do not see that in there in batch 0 and that was the analytics we had at that point in time.

Q. And in terms of the limit of detection, you agree that this type of equipment could have a limit of detection as high as 15 percent?

A. I can't comment on the equipment, sorry.

Q. Do you agree that if there is a 15 percent limit of detection, that means there could be up to 15 percent of something and you want to be able to determine --

A. Sorry I cannot comment on that. I am not the one who does those experiments. I'm not so familiar with that.

Q. You know there is a limit but you are not sure about the details. Is that fair?

A. That's fair.

Q. When we are talking about batch 0, we can look at the tests that you did, you just talked to us about, but do you still have the batch 0 today?

A. I am no longer with Grunenthal so I haven't got any batches from Grunenthal with me today.

Q. Fair enough. Did you receive the sample back after you sent it for testing, for the test you showed us?

A. I can't remember. So, we sent so many samples, I can't remember if I returned that particular sample.

Q. Isn't it true the last time you saw batch 0 when you tested was when you sent it out to the lab and they sent back

this result you talked to us?

A. As far as I remember, yes.

Q. So, if the defendants in this case, if they wanted to look at that sample and test it, you agree that is impossible?

A. Sorry.

Q. This litigation that's going on right now, we are here to talk about at trial, you will agree with me that the defendants, these are the parties that are present before you, could not test that sample even if they wanted to.

A. I don't know because I don't know if the sample has been returned to Grunenthal and where, if it has been returned, where it has been stored or whatever. I don't know. I can't tell you about what the defendants could do.

Q. You don't know anything about where batch 0 went after the test was done?

A. I can't remember.

Q. Now, when you were talking in your testimony yesterday, did you compare the steps made to form batch 0 versus the example 25 in the patent?

A. I'm not an organic chemist and I can't remember doing that in detail.

Q. And DTX 972 is the version -- and I know you prefer a hard copy. I'm sorry, this is not in the binder. I am referring, sir, to the German version of the lab notebook that's DTX 972. It's not in your binder.

MR. ALY: So, your Honor, if I may approach and hand it.

THE COURT: Yes, please do.

THE WITNESS: Thank you.

THE COURT: I'm sorry, what's the English version?

MR. ALY: DTX 974.

THE WITNESS: It's hard to read.

THE COURT: Is it D or P?

MR. ALY: It's a D, D974.

THE COURT: It's in which volume?

MR. ALY: Volume one. The cross binder. We are now shuffling many, many binders. Apologies.

And, your Honor, I'm being reminded this was the loose one the, late edition that was inserted into the pocket and I should have said that earlier. And I thank co-counsel for reminding me.

THE COURT: Okay. Thanks.

MR. ALY: Apologies.

THE COURT: Not a problem.

MR. ALY: May I proceed?

THE COURT: Yes.

Q. Dr. Gruss, on the top right there's the batch number BU 322-1-1. Do you see it?

A. I see.

Q. This is corresponding on the top right. It's zero, zero, correct?

A. It's refers to what sir, zero?

Q. Zero, zero right above.

A. Zero, I don't know what that means.

Q. You don't know if this is even the lab notebook that goes with batch 0?

A. I have not written this document so I don't know.

Q. Right. So when you were looking at the tests for batch 0 and telling us yesterday that batch 0 was Form B have you ever seen the process by which batch 0 was made?

A. As far as I remember I might have seen, I think I said that yesterday during maybe in the presentation in the company presentation.

But, I am not an organic chemist and as far as I remember it was not compared, the synthesis step by step. And I said that that batch 0, the results of batch 0 indicated for us that it's stable. Yes.

Q. So you can't say whether batch 0 was done in the same way as example 25 in the '593 patent?

A. As far as I know it was similar or at least, yeah similar to example 25.

Q. And that batch 0 that didn't have a melting point that they were able to obtain at Grunenthal, correct?

A. I don't know. I have not been at Grunenthal at that

point in time. I don't know who investigated any testing on that sample and how they did it.

Q. And what's reported here on the notebook page DTX 973 and German 9P2 and sinter point at 123.1, do you see that, degree celsius?

A. I see.

Q. And you know that a sintering point is different than a melting point, correct?

A. I don't know.

Q. You don't know?

A. I don't know what sintering point.

Q. You know that a sinter point is when, this is a transition that you can observe, in a material solid going to liquid but it's muddy or still resilient?

A. I don't know what sinter point.

Q. The number you will agree with is 123.1?

A. There is a Number 123.1.

Q. In English or the German, it doesn't say melting point, it says sintering?

A. It says also FP and I also under FP as fess point (sic), solid point.

Q. Thank you. So that's what I want from here is when you are looking at this exhibit, you don't know whether batch 0 was made according to the steps in example 25 of the '593 patent?

A. As I said before I have never did the comparison step

by step.

Q. So general questions now. You gave us a comparison yesterday of a graph comparing the batch 0 to your reference you called it CEPM 1A, right?

A. I call it as a reference pattern that was you mean the slide that was on the screen earlier.

Q. Yes, PTX 1547. Did you compare in that slide or any other slide, have you done a comparison of how that would look compared to a reference for Form A?

A. As I told yesterday to the Judge that I might have also compared at that point in time that was Form A in order to make sure that there's no form A in it.

I'm quite sure there's a little because I'm very, yeah, I try to be as precise as possible, yes.

Q. I'm just making sure. That's not a document you shared with us yesterday?

A. Generally the procedure was that I had data in Xcel file and put them and I might not have printed every comparison I did.

Q. You don't know even if that file comparison of the batch 0 to form A actually still exists?

A. I don't know what exists at Grunenthal. I don't know.

Q. And you didn't compare batch 0 results to batch one using XRD because you don't know even know what batch one is?

A. I can't remember. I have compared so many batches and

samples, I can't remember if I also had data of batch one. As I said, we try to get information on as much batches and samples that we could get in order to compare, in order to get an overview and an understanding what was going on.

Q. And another test that you spoke with us yesterday about was Marita Mueller's work, correct?

A. You talked about the resynthesis yesterday.

Q. By resynthesis you mean that Marita Mueller was trying to do the steps in example 25 of the '593 patent?

A. I was know, how should I say this, so, I knew that there was a re-testing of the procedure ongoing that was ongoing by Marita Mueller. We agreed with her.

Q. But you didn't supervise?

A. No.

Q. In terms of how that process was done, you didn't talk to Marita Mueller about that?

A. No.

Q. Marita Mueller is still employed at Grunenthal correct?

A. To my knowledge yes.

Q. And when she was asked to make example 25 at that time that was in 2002, 2001, is that correct?

A. Maybe we can look at the slide. It must have been in that time frame yes.

Q. Your demonstrative one may have the 2001 time frame.

A. It says September 2002.

Q. At that time Miss Mueller didn't have much experience in making compounds, did she.

A. She was a technician and Carsten Griebel supervised her work. And Carsten Griebel was an organic chemist Ph.D. chemist working at Grunenthal and he supervised the work as far as I know.

Q. The person who actually mixed the ingredients and followed the recipe, Miss Mueller, she didn't have a Ph.D. right?

A. So that's general procedure that in Germany technicians do the work that is supervised by a Ph.D..

Q. And I just want to make sure, did Miss Mueller have a Ph.D.?

A. Not to my knowledge.

Q. When you say supervised the work, do you know if Carston was reviewing the work in the same room while Miss Mueller was preparing?

A. No, I don't know how they communicated. But, generally so the situation in Germany is I think a bit different than that in the U.S. So people are generally well educated. They get an old profession which is called in Germany ausbildung and so they get the training on the, yeah, how they have to do their work. How they have to read instructions. How they have to follow instructions.

So they are well educated and they are dedicated in

order to do this type of work.

Q. I'm not saying Miss Mueller wasn't qualified to do her work. I'm asking was she qualified to do this work. I am asking about that though because in this case because she was asked to replicate an example. But, her job day to day was not synthetic chemistry at that time. Would you agree with that?

A. To my knowledge Miss Mueller's daily work was to get instructions by a supervisor, follow those instructions based on literature, based, might be on ideas he just developed in order to perform those operational work at the laboratory.

So I think that was part of her daily work doing and following instructions. It's my understanding at least.

Q. Of course. Would it surprise you that if the instructions she was following day-to-day were titration experiments, measuring and adding liquid as opposed to synthesis?

A. At what point in time?

Q. At the time she was asked to do this replication project on resynthesis?

A. To my knowledge so that my understanding of the job of Marita Mueller at that point in time, she was already working on synthesis work earlier. That was my understanding at that time at least.

Q. Do you know, can you tell us how many compounds she had made before making the Tapentadol?

A. I don't know when Miss Mueller joined Grunenthal so I can't tell you. And I don't know what her workload was. I was not responsible for her.

Q. Let's look at her lab notebook page together for the work that you talked about yesterday. That's on DTX 1003. It is in the binder.

A. I put this 972 in there.

Q. Yes, you can return that. Volume one should be DTX 1003.

A. I put it in 974.

Q. And just before we start looking at the document, I want to ask you when Miss Mueller finished the work that she did and it was sent to an x-ray diffraction lab, what color was the material?

A. I don't know.

Q. Would you be surprised if it was mustard yellow?

A. I don't know. I am not an organic chemist.

Q. So, were you the one responsible for taking the Mueller result, whatever compound she got, and sending it to the lab?

A. I don't know if I -- as far as I know I wrote the letter to send the samples, yes.

Q. So when you were writing the letter to send the samples, did you yourself actually see the samples you were sending?

A. I can't remember.
Q. You don't know? It could have been any color. You just don't remember?
A. I don't know if I seen that sample. So the procedure was that generally the samples have been packed so it may be later stage in time if somebody packed the sample and sends it and I wrote the letter to the contact person.
Q. And you sent two samples from Grunenthal to the lab to be tested for the Miss Mueller samples, correct?
A. As far as I remember, it has been two years, so I wrote the letter with the batch numbers.
Q. Do you agree one of them was yellow in color and one of them --
A. I done know the color.
Q. So, if Miss Mueller put in her lab note and testified at deposition that one was yellow colored and one was beige colored, you don't disagree?
A. If she testified that, she might have seen the samples.
Q. When it comes to the idea for hiring a company to do the XRD, you hired a lab to do that, the x-ray tests, correct?
A. So, Grunenthal had two universities doing the work at that point in time in the 2001 , 2002 timeframe before --
Q. And Grunenthal, because of its size and stature in the country, had a lot of connections with labs and even universities to do different kinds of work, correct?

A. I don't know what Grunenthal has.
Q. Now, Grunenthal didn't ask at anytime for a lab, outside lab to try and replicate example 25, correct?
A. I don't know what Grunenthal did with that.
Q. Let me ask you, had you ever seen results from somebody outside of Grunenthal, independent lab, trying to replicate the steps of example 25 as reported in the '593 patent?
A. Not to my knowledge. I haven't seen that.
Q. Now, as a result of the work that you were compiling at Grunenthal once you got there -- now, I want to shift subjects to a patent that you submitted to the Patent Office, the '364 patent.
You're familiar with that, correct?
A. Yes.
Q. Let's look at the '364 patent. It's DTX 304.
A. So that's in the other binder as well.
Q. That should be in the first volume, same binder we've been in.
A. DTX 304.
Q. 364. 304. You're right. '364 patent is 304.
A. So, I'm confused. So, it's DTX 301 here then the next is DTX 31.
THE COURT: I have the same.
Q. Let's use the plaintiff's version. I think sometimes we tried to keep, though the binders are large, sometimes we

were using the plaintiffs PTX 309.

A. PTX 309. Mine starts with PTX 04911.

Q. Let's give it a third try is a charm, sir.

MR. ALY: And your Honor with apologies.

THE COURT: Not a problem. What is it?

MR. ALY: Volume 2, PTX 309. But it's volume two of today's binder.

THE COURT: What is it again?

MR. ALY: PTX 309.

THE COURT: That worked.

THE WITNESS: Yes, for me as well.

Q. Let's reset ourselves to make sure we're looking at the same thing.

We are talking about the '364 patent, one of the patents in this case, right, Dr. Gruss?

A. I can hardly read this copy so you have probably better than I. I don't know. How is yours?

Q. Plaintiffs are suggesting to use PTX 1458 instead of their PTX 309. But to do that that would be again in their binder 1458. How many times the patent can be referenced, we will find out.

THE COURT: I guess not enough.

MR. ALY: Never enough. Can we charge this time to the copy vendor?

(Laughter).

A. 1458 yeah it's better to read.

Q. Thank you, sir. So, Dr. Gruss, the '364 patent that's at issue in this case, correct?

A. I see this '364 patent.

Q. All right. And let's go to example two which is on column five. And example two says, it's title is preparation of form A.

Do you see that?

A. Preparation of form A.

Q. And the preparation of form A, the first step in that, in the '364 patent refers to the Tapentadol hydrochloride being prepared according to example 25, correct?

A. I see that.

Q. And example 25 is referenced here as a European patent but that is the same as example 25 in the U.S. patent. You're familiar with that, right? Is that yes?

A. Yes.

Q. And there's a procedure that's given here for what to do with that starting sample and the result reported in your patent is crystalline form A, correct?

A. The purpose of the procedure was to provide form A yes.

Q. For the starting material though you didn't write in the patent what the starting material was, correct? You just said it's whatever was formed with example 25.

A. So for me it was important to start with Tapentadol

hydrochloride, yeah. It was dissolved. And then afterwards it was crystallized. And then form A comes out. That was the procedure that we described here. And yeah, the purpose was to provide a way to get form A.

Q. So you agree you didn't explain what the starting materials polymorphic form was, correct?

A. So for me it was not of relevance because it was dissolved afterwards and then the crystallization procedure was described here. And the outcome of the crystallization procedure is form A.

Q. And the explanation to the Patent Office you're giving is start with some Tapentadol hydrochloride unknown form, as far as the patent office knows, do a procedure and get crystalline form A.

Is that correct?

A. What I said is so I understand it is start with Tapentadol hydrochloride, follow the procedure, and yeah with that --

Q. To be clear, though, very clear, when you're saying that there is starting material prepared according to example 25, that was not work that Marita Mueller did, correct?

A. Sorry, I did not understand that.

Q. Absolutely. It's very important.

The work that it says here that was the starting material prepared according to example 25, that was not work

that Marita Mueller did that was used in this procedure?

A. I don't know.

Q. You don't know.

A. So, I don't know. As far as I know I think this example comes from SSCI. I'm not sure but --

Q. Well, let me just make one thing clear. The starting material there were 32.2 milligrams of it, correct?

A. I see that.

Q. Miss Mueller never made 32 milligrams of a material?

A. That does not necessarily say that you take the whole batch that was once produced in order to do investigations, yeah.

You start with a batch, take a bit and do your experiments. So that does not tell you anything about the batch where it comes from. So the purpose was here to provide a method to get crystalline form A. And as I mentioned, the starting material has been dissolved. It loses formation before the crystalline state, for example when it was dissolved, and then it was crystallized.

Q. To be clear, this could very well be Marita Mueller's material that is the starting material here for example two you're saying?

A. No, I'm saying that I understood it to start with Tapentadol hydrochloride, take that amount of Tapentadol hydrochloride, dissolve it and follow the procedure and then

you get form A.

Q. But right now I'm asking you the source of that starting material that was prepared according to example 25.

Can you swear today that it was prepared by Marita Mueller?

A. No, I don't know where it comes from.

Q. Can you swear whether or not it was batch 0 material?

A. I don't think that it was batch 0 but I don't know.

Q. And what you're telling the Patent Office is you take the starting material but you didn't tell the Patent Office what the starting form was of that material, correct?

A. Form B. It was not of importance because you dissolve it afterwards then the formation about the crystalline state is lost. Yeah.

So, it gets dissolved. It gets surrounded by solvent molecules. And it's no longer surrounded by its own names. And that's what crystalline forms are substituents that in every direction you have the same molecules around. And when you dissolve it yeah, it gets distributed.

Q. What you're saying is that when you put a solid into a liquid and make a solution, there are no crystals anymore? Is that right?

A. The information about the crystalline state is gone and then you, yeah, whatever method you apply, either you cool it or you remove the solvent, then it crystallizes out or

precipitates, depending on the procedure.

Q. But Dr. Gruss, simply put, it isn't true that your invention that you are describing to the patent office is starting with form A, doing something to it, and ending with form A?

A. No.

Q. You don't think so?

A. I don't think so. So this was I understand this example as start with tapentadol hydrochloride, dissolve it and follow the procedure and you get form A. That is my understanding of that example. And the purpose was to provide a method to produce form A, to produce form A.

Q. Isn't it true that the starting material though was form A?

A. Not to my knowledge.

Q. Let's walk through the document DTX 144. These are interrogatory responses that were presented in this case by your representatives on Page 7?

A. DTX?

Q. DTX 144. And I'm looking at Page 7 of those interrogatory responses. Number 21 is the request on the bottom.

The question presented was tell us the information or where these examples in the '364 patent came from.

A. Sorry, can you maybe try to explain to me where this

document comes from. I have not understood it.

Q. Not at this time I'm not going to do an explanation. But, I will ask you about the data. If you don't understand it, you can let us know that.

A. Okay.

Q. Now on the next page or Page 9 of the Document, 2 pages in, there's a response to the material. And it's, let's look at the top. And the response is that documents that support examples 2 and 3 of the '364 patent can be found at, and there's a lot of numbers presented, right, but it includes this range between 1090 and 21277 and three pages. Do you see that?

A. Yes, I see that.

Q. And let's keep that on the left side of the screen and bring up the documents so we can look at them together. Let's call up that's going to be DTX 1001.

DTX 1001, this was a report that was provided to Grunenthal in 2006, correct?

A. So the front page shows Grunenthal front page and the title says polymorph screen. I see that.

Q. On the bottom right of that page number there was a small number all the way on the bottom right GRT NUC C21090. That's the same number that's in the interrogatory response on the left of your screen correct?

A. I see that.

Q. And now if you will go to the page where it's the

interrogatory response is saying, look at for example two. If you want to see that what I am looking at, 21094. So we will go forward a few pages in Exhibit DTX 1001 to 21094. And in particular there is an experimental introduction and summary.

So do you see that it says for the sample CG 5503 sample received from Grunenthal is summarized in Table 1? Do you see that?

A. I see.

Q. So what it's saying from the record from SSCI here is that if you want to know what form of material we got, look at Table 1, correct?

A. No. What the document says it says the sample that we sent to SSCI are stated in Table 1. But SSCI did its own experiments and, yeah, might have used their own samples for further experiments so --

Q. Let's look further at the next page referenced in the interrogatory response 21103. Let's look at first the Table 1. That's Page 21094 asked us to look at Table 1 that happens to be on 21102 on the very top Table 1.

A. Table 1.

Q. We don't know Table 2. Just one.

A. Just Table 1. Yeah.

Q. And Table 1 clearly reports that the sample received had an XRD result of A, correct?

A. I see that. So as I mentioned before that was their

testing I suppose. And at that point in time they tested as A.

Q. Whatever SSCI got at this time, which the interrogatory said, that is what relates to the patent examples that's form A, right?

A. It says so there were many numbers listed and it refers that this is one document. But it does not necessarily mean that this batch has been introduced in the example two. So that's not my current understanding.

Q. Trust me we will look at the other pages. But right now I want to make sure there was only one sample lot that was received by SSCI. That's what they are telling you?

A. I see that.

Q. And that one lot that they received was form A. That's what they are reporting?

A. That was their testing at that point in time. But, it does not exclude, as I did additional experiments, do further experiments for their further work.

Q. As you said the interrogatory response did have a couple of other pages, 21103 was the next one.

A. 21103.

Q. And that's Table 3. Do you see that?

A. Not yet. Table 3, yes.

Q. And in Table 3 there is a report of a polymorph screen where they take the input material, put it through different conditions and then report on a result, correct?

A. That's what the table says is they did several experiments. They did not -- as far as I don't see what material they took in order to perform those experiments.

Q. Dr. Gruss, they only had one set of material to use. They only had one lot of material to use as the starting material?

A. But I don't know if they exactly put that material into the experiments or if they took other material that they have processed further and then took that material. But that's not stated here. So the batch is not listed. I can't see that in the table.

Q. And I'm just asking you based on the interrogatory response we received from the law firm representing Grunenthal, the test result that was shown for all of the conditions had at least -- had form A in it. If any sample or solid could be detected, it always had form A in it?

A. So, the results from this particular, which is just an extract of the experiment and then just a snapshot says that mixture of A and B have been performed and also experiments where no solid was present.

Q. And it goes on to the next page. To be fair, Table 3 does but still again all of them whether there is any solid present are form A.

A. There is a mixture of A and B as well. And this is just a particular experiment of all the numerous experiments

SSCI did. They did other experiments where B was the outcome.

Q. There was another result but you do say there were different experiments that were done where B was the outcome.

But for purpose of the '364 patent, that is the only report from which the data in the patent comes from. Isn't that true?

A. I don't know. I don't know where the data comes from. That's what the law firm states.

Q. This is what we are seeing in the response on the top, it's still there, that the data for the 2 and 3 only come from this one document which is the entire range of the document for DTX 1001. And it identifies these three individual pages.

A. It gives a whole range of pages 21092 and 21277 including those two pages that you just mentioned.

Q. DTX 1001 has the first page of 21094 and the last page is 21277, right?

A. Sorry, it was a bit too fast.

Q. No problem. Can you just, I just want to make sure we are looking at the same thing. The last page in your document DTX 1001, and I see you're turning to it.

A. 21277, okay.

Q. That's the same as the number on the interrogatory response, correct?

A. Yeah.

Q. All right. Now, the next and final number that we're

asked to look at in the response is 21136. And if you look at 21136, which is Page 47 of the PDF 21136, there is a lot of XRD data results, correct?

A. I see it.

Q. And on the top right of that is a reference Number 631-03-02, correct?

A. 6310302, yeah.

Q. Now we'll go back to Table 3 which was on 21103 of the document.

A. Okay. Yes.

Q. And we'll look at the very top row, top two rows with the acetone portion and that number is right there 6310302. Do you see that?

A. Yes.

Q. And the condition is SE, right?

A. Yes.

Q. And the solvent is acetone, correct?

A. Yes.

Q. And in terms of the result, it's form A that's presented, correct?

A. Yes.

Q. And this is, the data is acetone and the condition results in form A. That's in example two of the patent, correct?

A. I need to compare that in order to --

Q. We will do that right now. But, let me just take the three steps and then we will be able to take those three steps and look at the patent.

The first step of the solvent is acetone, correct?

A. I see.

Q. The second is SE which is slow extraction, right?

A. No.

Q. Let's look at Table 3. Beneath the table is a legend, slow evaporation?

A. That's correct.

Q. I apologize. You're right. Slow evaporation. And then result of the acetone solvent, the slow evaporation is the result of form A?

A. I see that.

Q. Now if we can look at the patent I think the one we are agreeing upon is PTX 1458 example two in column five.

A. I see that.

Q. In the preparation here what we are talking about here is dissolving in two-milliliters of acetone, correct?

A. Yes.

Q. And then the solution was left to crystallize by slow evaporation, correct?

A. Yes.

Q. And the result is crystalline form A, correct?

A. I see that? Twenty two.

Q. In terms of reviewing the material in the interrogatory response as we just walked through the whole process, the only material they had to start with at SSCI was form A, correct?

A. So the outcome of the experiment was form A and the purpose of the experiment we provided was form A. So since the crystalline material, as I explained, further has been dissolved, it was for me not of interest what the starting crystalline form was.

Q. But that's what I want to make sure. Do you agree with me, now that we've gone through the documents, that actually what's shown in the example two is you start with form A and you end with form A?

A. No. I'm still not on this side because I am -- we are at Table 3. So the Table 3, so what you show to me in Table 3 was the outcome of the experiment form A. That's correct. And in Table 3 nowhere states what the starting material was.

Q. The starting material, sir, isn't that already provided in Table 1?

A. That is the material that we sent to SSCI. But, I don't know if they exactly, since I was not there when they performed the experiment, if they took exactly the material or if they have maybe performed other experiments what happened, was then was the material put under the conditions listed in the table, I cannot tell you. I can't draw the conclusion from the material we sent to what was actually put in that

particular experiment.

Q. Let's just look together at what SSCI said. DTX 1001 Page 7 of the report, Page 9 of the PDF.

A. Where are we now?

Q. 1001, the document we were looking at a moment ago.

A. Yes.

Q. Page 7 of the report which is 21098 top section, section B.

A. All right. Sorry I'm not so fast. It's 121094.

Q. 21098.

A. 21098. Okay. And that's B what you highlighted on the top. Okay.

Q. What SSCI says for all the work they did for the table, for the polymorph screen, they write that the XRPD pattern of the material used to generate samples in the polymorph screen is shown in Figure 1 which was designated as form A, correct?

A. I understand that as being the original material they started with. But I cannot exclude that they did not do other experiments and use material from that experiment. I cannot exclude that.

Q. So when you are looking at the patent, as you sit here today, you can't exclude that all the samples started with form A and ended with form A?

A. No, I said what the purpose of the example was to generate form A. And the material, the starting material was

dissolved. So the information about the crystalline state was getting lost.

Q. While we are on the SSCI report -- actually let me shift because I know I am taking some time here and I want to move on. I will share with you the last document we will talk about and that's DTX 1242.

A. DTX 1242.

Q. And as we are transitioning to this last document for the '364 patent, do you know -- I'll ask you the opposite question.

Do you know of any example where you started with form B and then converted it into form A and that was --

A. Sorry, go ahead.

Q. Do you know of any example in the '364 patent where you started with form B and converted it into form A and that was the invention that you were reporting?

A. Yeah, I think so.

Q. Let me ask you this question because when you take form B and you have it at room temperature, it converts to form A correct?

A. No, it depends on the experimental condition under which you perform the experiment. So, as far as I remembered I have to make sure that there are experiments that are essential from which form you started but not in the example two, for example.

Q. That's why I want to go to DTX 1242. The first summary is the summary of polymorphism from 2005, correct?

A. That is a document from 2005 that might reflect the matter at that point in time. That document is written by, put together by Andreas Fischer. So that reflect his point of view.

Q. You know Dr. Fischer. He is co-inventor with you?

A. What?

Q. Co-inventor. He is also named as an inventor?

A. Yes.

Q. If you turn to Page 5 of the exhibit, there is a Phase 2 discussion. You see the Dr. Fischer, the other named inventor says that Form A goes to Form B under conditions of heat or grinding or milling. Do you see that?

A. I understand this presentation as a presentation for other people. And it might include over simplification in order to let people understand what it was generally going on.

Q. And Dr. Fischer also reports from going from form A to Form B, cooling to room temperature, return to form B, back to form A, correct?

A. That might not reflect the situation for every sample and every situation. So, as I mentioned, there are samples that do not convert to A at room temperature.

Q. For example, one of the things you asked SSCI to help you with is sometimes form B doesn't go back to form A right

away, you asked for an explanation for that, right?

A. To my knowledge we haven't yet fully understood how this works. And when it converts and when it does not convert. And we have results that show that it can sit there for long periods of time and I have no reason to believe that every sample converts back at room temperature from B to A.

Q. And the difference is examples with impurities don't convert back to A? Samples that don't have the impurities are always A, right?

A. As far as I remember, that is not the truth. But we have not yet already understood the impact of the impurities. And as far as I remember, there are examples with impure material with respect to impurities is A and more pure material is B.

So, as I said, we have not fully understood the impact of impurities.

Q. Let's take a look at Page 19. Page 19 is titled Impurity Profile. Do you see that?

A. Yeah.

Q. On Page 19 if you look on the right side modification, that's what Grunenthal is calling the form, there's two entries where there's only form B reported. Do you see that?

A. There's another form where it says mixture of A and B.

Q. And there's a mixture of A and B. Taking the amount of the impurities, do you agree with me that for CEPM 1A and CEPM

2A, those are the two samples with the highest reported impurities?

A. So Grunenthal as far as I know there have been other examples that have impurities. So this is just a snapshot and a short excerpt from the whole bunch of samples and the whole investigations with respect to this impurities impact.

Q. I'm asking you, Dr. Fischer thought it important, your inventor, to put these samples on this slide and it includes two with the highest impurities getting to form B, correct?

A. That might be in his understanding of the situation at that point in time.

Q. And for the next one you point out there's one with a mixture and that is actually where there's the next highest level of impurities that are reported on the table. And that results in a mixture of form A and B?

A. As I stated before, this is just an excerpt of a whole bunch of examples where we have investigated the effect of impurities.

Q. And all of the other samples, you agree, are form A?

A. No, not all of the other samples as I mentioned earlier. So --

Q. The ones reported here, you agree all the other ones reported on this page are form A, correct?

A. So, that are, as I mentioned before, that's a snapshot of the situation and of this series. And you see it's a series

of CEPM investigations. So one particular series of experiments, there the outcome was as it is presented here.

Q. And the conclusion that's drawn is that the impurities effect the formation of the unfavored modification form B, correct?

A. That was the understanding at that point in time, I suppose, from Andreas Fischer. And I mentioned earlier that the complete polymorphism studies undergo a long period of time and the understanding grows and you have hypotheses, you try to confirm them and then you find other results that disagree with your hypothesis.

Q. In 2005, this was the understanding?

A. I don't know. That was at least the answer Dr. Fischer put together. It might have been his understanding from the situation at that point in time.

Q. Thank you. I have no further questions.

THE COURT: Thank you very much.

MR. SCHULER: I should be pretty brief, your Honor.

THE COURT: Go right ahead.

THE WITNESS: Can I have some water?

THE COURT: Yes.

CROSS EXAMINATION BY MR. SCHULER:

Q. Good morning, Dr. Gruss.

A. Good morning.

Q. My name is Ken Schuler. I represents Roxane Laboratories. I'm going try and save some trees and just hand up a couple of exhibits, okay?

MR. SCHULER: May I approach?

THE COURT: Yes.

THE COURT: Any issue with the exhibits?

MR. GLANDORF: No issue.

THE COURT: No issue with the exhibits. Fine.

Let me ask you, I know there is an issue with respect to 1097. You didn't use it.

MR. ALY: I didn't use it.

THE COURT: Is anyone using it? No one's using it.

MR. SCHULER: I do not believe.

THE COURT: So the issue you had with respect to lack of foundation, the document hasn't been used.

MR. GLANDORF: Excellent.

THE COURT: All right.

Q. Okay. Dr. Gruss --

THE COURT: I'm sorry, just one last thing. Do you have any demonstratives that they need to take a look at?

MR. SCHULER: No.

THE COURT: Sounds good. Go ahead.

Q. All right. Doctor, is it fair to say that your work that led to the patent was work that would, that it's about

solid state forms of Tapentadol hydrochloride?

A. So as I stated my contribution yesterday, so it was not, it was also project management.

Q. It's just, I'm not asking about your work. I'm just asking, generally speaking, you were characterizing solid forms of Tapentadol hydrochloride?

A. And also producing them and supervising projects which lead to polymorphism, screen crystallization studies and that.

Q. Fair enough. Is it fair to say that Grunenthal was interested in investigating polymorphism for Tapentadol in part because of FDA guidance concerning that subject?

A. So, it was also important for Grunenthal to understand what was going on as such. And Grunenthal, you cannot tell Grunenthal such, so I was focused on the solid state and I was interested in doing that investigations.

Q. Okay. Let's just be clear on my question. My question was, in part, Grunenthal was undertaking the work that you did because of FDA guidance concerning polymorphism?

A. As far as I know at that point in time there was FDA guidance in place which was a recommendation to pharmaceutical companies to conduct investigations like that.

But there are other reasons to perform an investigation.

Q. I will come to that in a second. I just want to make sure we agree that part of the reason that Grunenthal was

interested in polymorphism of Tapentadol was the FDA guidance you just referred to?

A. I don't know it was really part of the reason. But at least we knew that there was in draft guidance documents. So I don't know what the purpose or the origin, if it really was a reason. It may be part of the reason. I don't know.

Q. Okay. One of the documents in the first binder should be DTX 286 which I believe is your deposition.

A. DTX.

Q. DTX 286. And if you could open it to Page 68.

A. Wait. First I have to find it.

Q. Starting at Line 4. Do you see the question, Dr. Gruss, was why was Grunenthal --

A. Sorry I'm on what page are you?

Q. Please open to 68.

A. What document is that?

Q. DTX?

A. Yeah, yeah, yeah but what is it about?

Q. This is your deposition transcript.

A. It's mine.

Q. All right. Are you at page --

A. Yes, 68.

Q. Are you at Page 68, sir?

A. I'm on the 68 yeah.

Q. If you look at Line 4, the question was Why was

Grunenthal interested in investigating polymorphism for Tapentadol when you joined the company?

A. Yes.

Q. Answer: To my knowledge, there was an FDA guideline?

A. The guideline.

Q. That was one reason. So, pharmaceutical companies have to take consideration of polymorphism when they are developing pharmaceutical compounds. That's a regulatory issue. And another point is that from a, a process point of view. So if you want to know what's going on in the process.

Did I read that question and that answer correctly, sir?

A. Yeah, yes. As I mentioned yesterday, I'm not a native speaker so I might not have found the right words. So the guideline recommendation --

Q. That was not my question. My question was did I read that question and your answer correctly.

A. Yes, as it's stated, yes.

Q. Now, sir, the regulatory issue that was associated with polymorphism was motivating Grunenthal to do this work, correct?

A. My understanding today is that it's FDA guidance is just a guiding document. That's a guideline.

Q. I didn't ask that. Do you recall that I asked you?

A. No. Please repeat your answer, your question.

Q. Sure. My question was, that guidance was motivating Grunenthal to undertake this work, correct?

A. Could be.

Q. I think you said on cross-examination that you wonder whether the transit of the samples to, was it Indiana?

A. Sorry, SSCI is in Indiana, West Lafayette.

Q. And you kind of suggested that the transit might have effected it?

A. Might be.

Q. Why did you choose an outfit across the ocean to undertake this screening with the knowledge that the transit itself might impact the polymorphic form?

A. That's not of importance for the polymorph screening, the starting material for polymorph screen is not really so important. Because you undergo several investigations with that material. You dissolve it. You recrystallize it.

So the reason to provide material is just to provide them with Tapentadol hydrochloride in this particular case.

Q. Did you take any steps to insure that the samples that you sent were shipped appropriately?

A. What you mean was shipped appropriate? So I was not responsible to pack the material. I was not really familiar with all those documents that were requested for shipping the samples .

So, as I mentioned in the case of Marita Mueller,

people are educated and trained and handle according to the requirements when they send samples as well.

Q. So the steps you took were to train people appropriately. Is that fair?

A. Sorry.

Q. The steps that you took were to train people as to how to appropriately pack the samples?

A. Not me. People are also trained by other persons which are familiar with the matter. And at that point in time there was not really a consideration of yeah and also probably not an understanding how the different conditions can alter the crystalline form.

Q. Okay.

A. And I don't know if there has been any provisions with respect to polymorphism.

Q. Fair enough. Now, on direct examination you testified about some example disposition that occurred in the year 2010. Do you recall that?

A. About what, example?

Q. Destruction or disposition. I'm not sure which word you used.

A. I think I said samples have been disposed like according to the law they have to, they are treated so that they can't do anymore harm to public or people, that the material cannot be recovered.

Q. Okay. And I just want to understand what you said. I think you said you took samples of Tapentadol hydrochloride that had been studied as part of your work and you gave them to the people who are in charge of handling controlled substances?

A. No, I did not do that personally. So what I said yesterday, first of all, samples are used regularly, analytical techniques, methods, they are used. Then we tidy up in the laboratory. The samples are already in place. And at one point in time you try to dispose them.

And the other point I mentioned yesterday was this, when Tapentadol hydrochloride becomes a controlled substance, it was with respect to that and the regulatory requirements were disposed.

Q. And this was in the year 2010 that you disposed of those samples?

A. It was not me but it was part of the -- not all the samples of the project have been disposed.

Q. Okay. So some samples were retained even though this change in the law occurs. Is that your testimony?

A. This is, the point is --

Q. I don't want the point. I want your testimony. Some samples of Tapentadol that you used in your polymorphic work get retained? Yes or no?

A. Tapentadol source that we proceed --

Q. Sir, yes or no?

A. There have also been samples that have fallen under this consideration and I can't remember exactly if there has been Tapentadol hydrochloride samples being retained. But I know from other sources they have been retained.

MR. SCHULER: I ask that that answer be stricken.

THE COURT: Did you say source or other salts?

THE WITNESS: Source, source. Like the regulation when Tapentadol became a controlled substance, it was not just Tapentadol hydrochloride, but also other yeah, molecules that are similar like other salts, hydrochloride might be hydrobromide things like that, where we get bigger material that it was worse to keep up, we retained that because it had to be stored in the safe and not, cannot be just stored in the laboratory.

THE COURT: I'm not going to strike it. Ask it again. State it simply.

Q. Were samples of Tapentadol that you used in the polymorphism screening retained even after the disposition of of other samples?

A. I don't know if any samples has been retained. I don't know.

Q. Now, is it fair to say that you don't know whether or not you saved or destroyed any samples of this batch 0 of Tapentadol?

A. So, as I stated earlier, I can't remember if we have

returned that sample. So yesterday it was said it was just a tiny amount of sample and I don't know, I can't remember if I received that back. If I have received it back, I don't know where it has been. If I return it to, I can't, I don't know. It's too long ago.

Q. Okay. And so the answer to my question is you cannot remember one way or the other whether batch 0 samples were disposed of in 2010?

A. In 2010, I don't know. I don't know. It might have been earlier. So in the time frame 2001 already or 2002 I don't know even if I have that samples received back.

Q. Fair enough. All right. Let's move to the patent which is PTX 1458.

Mr. Haw if you could put up column one starting at the bottom, sir.

I want to look at the sentence that you looked at with your Counsel on direct examination.

A. Column one?

Q. Correct. The very last sentence I believe is column one, is that the sentence you discussed with your Counsel on direct examination?

A. The last sentence, I think it was that one, yes. This is it, uh-huh.

Q. And there are different aspects of polymorph stability, correct?

A. In that sentence you mean?
Q. Just in general.
A. So in general there are a lot of aspects that are relevant with respect to polymorphism.
Q. And one aspect of polymorph stability is called thermodynamic stability?
A. That's correct.
Q. That refers to the energy that's required to dissolve the crystal matters of the polymorph correct?
A. No.
Q. Is it true that the more thermodynamically stable a polymorph is, the more energy it takes to dissolve that crystal lattice?
A. So the dynamic has to be considered with respect to the conditions under which the thermodynamic, the more stable indication. So with respect to Tapentadol, it depends really on the temperature where you get it.
Q. Fair enough. But at any given set of conditions it's fair to say that the more thermodynamically stable a polymorph is the one that will dissolve slowly, correct?
A. No. From my understanding the most thermodynamically modification just states that the crystalline state in which it sits is more stable than the other. So it has a lower energy.
Q. And can we agree that using the polymorph with the highest thermodynamic stability is not necessarily, in and of

itself, valuable? You might actually want the less stable polymorph?

A. That depends. And as I stated before, it depends on what conditions, what is the purpose, so that it's not a question that can be generally answered.

Q. Can we agree that high thermodynamic stability may have disadvantages in terms of bioavailability?

A. Sorry, can you please repeat the question?

Q. Sure. Can we agree that high thermodynamic stability may have disadvantages in terms of bioavailability?

A. First of all, I don't know what you mean with high thermodynamic stability. And I don't think that it's really a disadvantage so --

Q. Let's look at what you said on that subject in the past.

A. And also always depends on the case you are looking at.

MR. SCHULER: Your Honor, can I approach the witness?

THE COURT: Yes.

THE WITNESS: Thank you.

Q. We've marked this for identification as, I think, DTX 2001.

THE COURT: I'm sorry, any issue? Any issue? Are they just getting it for the first time?

MR. SCHULER: No. They are just getting it for

the first time.

THE COURT: Anything on this?

MR. GLANDORF: No objection.

THE COURT: Thank you.

Q. You are familiar with that patent application, are you not, doctor?

A. Yes, I note it.

Q. You are the sole named inventor on this patent application, correct?

A. Yes.

Q. And it was published in October 9th of 2008, correct?

A. It was published date October 9, 2008, yes.

Q. If we can turn to the page marked one and there's some paragraph numbers.

And I'd like you to call up, Mr. Haw, under Paragraph 5.

Q. And in Paragraph 5 you wrote on the one hand high thermodynamic stability is usually associated with good stability and storage but may have disadvantages in respect to bioavailability and other pharmokinetic parameters.

Did I read that correctly, sir?

A. So at least the publication says that.

Q. And then it says Thus high thermodynamic stability usually correlates with relatively low solubility.

Did I read that part correctly?

A. That's stated there.

Q. Okay. And that refers to what I said earlier which is that the more thermodynamically stable a polymorph is, the more time it takes and energy it takes to dissolve the crystal mass, correct?

A. So that too, no, that's not correct.

Q. Okay. That's all I need to know, sir.

If we go to Paragraph 6, pull that up, and in the middle -- I'm sorry, you say on the other hand good solubility is usually associated with good bioavailability.

Did I read that correctly?

A. Yes.

Q. And then the second sentence says Thus good solubility usually correlates with relatively low thermodynamic stability. Is that right, sir?

A. That's stated there.

Q. Okay. Now if you could turn to --

A. Also I want to stress that says usually and so --

Q. Okay. So then yes it says usually. I didn't say any other word, did I?

Let's turn to Paragraph 23 on the next page.

A. Twenty?

Q. Twenty three. And the second sentence here you say usually, however, solubility decreases as thermodynamic stability increases.

Did I read that correctly?

A. Yes.

Q. Now, another form -- let's go back to PTX, the patent 1458. The same statement we were looking at in this sentence does not specify thermodynamic stability, does it?

A. That sentence says it is very stable at ambient conditions.

Q. I'm just talking about the sentence you talked about with Counsel. Okay. There are other attributes of stability for polymorphs like chemical stability, correct?

A. Please repeat the question.

Q. Sure. Another attribute of stability with regard to polymorphs is their chemical stability, correct?

A. No, with polymorphs you see it's more that you are not looking really at. That's one part is the chemical stability. But it's more important also to have as the physical, chemical parameters like change in the behavior. It's not really only chemical stability.

Q. I didn't say only. I just said it's another form of it, correct?

A. Yes.

Q. Okay. Now, Grunenthal actually studied what we looked at in our patent which is our patent application which is the potential for polymorphic thermodynamic stability to impact bioavailability.

Do you recall that study?

A. No.

Q. Okay. Let's see if we can refresh your memory. It is DTX 1158. It's one of the few I handed to you, I think.

Do you see that this is a research report? And I believe it's from June 23rd of 2003.

A. So, the title says so prepared by Fischer June 2003.

Q. I was looking at the form at the top.

A. Yes.

Q. So the record here is CG 5503, that's Tapentadol?

A. That's Tapentadol. That's a synonym for Tapentadol hydrochloride.

Q. Thank you. The title is Summary of Polymorphism Investigations for Tapentadol hydrochloride.

A. It seems to state the stages and the understanding of that investigation at that point in time.

Q. If you could turn, Mr. Haw, to Page 14 of the exhibit. Call up Table 4.

A. Fourteen.

Q. It has solubility data?

A. Sorry, I'm not there yet.

Q. Table 4. I'm just reading the title, Solubility Data of form A and B in different buffer media.

Do you see that?

A. So, I see table, yeah, I have it. So let me have a

look.

Q. Sure. It's just so that there is an answer to the pending question, it just simply says the title of Table 4 Solubility Data of form A and B in different buffer media?

A. That's it.

Q. And the first one that's listed is simulated gastric fluid. Do you see that?

A. Yeah, I see that.

Q. What would be the idea for studying gastric fluids or simulating gastric fluids?

A. I am an inorganic chemist, but I know you have to apply several media to see how the compound or the solubility of the compound is.

Q. The ph here is very low, very acidic?

A. Yes. And that's to simulate the human stomach. As far as I know we have gastric fluid -- I am not really familiar with the medical terms, but I think its ph could be.

Q. Very well. And the values are expressed in what you would call milligrams per millimeter, correct?

A. Yeah, they were similar.

Q. And to polymorph A, thesolubility is as listed 388-milligram per millimeter, correct.

A. It's solubility and not the dissolution. So you also referred to earlier on the speed of dissolution, and that's solubility.

Q. This is an absolute value?
A. That's a value, yeah, when you have dissolved it, then you determine the solubility.
Q. And then for polymorph B, the corresponding value under the same conditions is 394, correct?
A. It's a bit higher, yes.
Q. Yes. That's what I wanted to get to next.
If we can go to the text underneath the table, it says in fact the second paragraph says solubility is very high for both polymorphs, correct?
A. Yes.
Q. And the summary of the data in the fourth paragraph that is summmarizing this data, an influence of the polymorphic form on the drug release of the finished product is most unlikely.
Do you see that?
A. I see that sentence.
Q. Now, can we agree that 388 versus 394 is virtually identical?
A. The other one is higher.
Q. Understood. But it's virtually identical?
A. The document solubility is very high. That was the conclusion under Dr. Fischer.
Q. This data table does not appear in the '364 patent. Can we agree on that?

A. I haven't seen that. And it was, I haven't seen it. I haven't seen it in the patent.

Q. And can we agree that this data was available to you and your colleagues that are the listed inventors years before the patent application was filed?

A. I don't know that I knew about the data. The document was written by Andreas Fischer. He is one of the co-inventors but I can't remember knowing about it. I don't know.

Q. Okay. Can we agree that Dr. Fischer wrote about it over a year before the patent was filed?

A. I think so, yes.

Q. Now, can we agree that if this data was in the patent, that it would tell a person of skill in the art that there is virtually no difference between polymorph A and B in terms of a pharmaceutical finished product used in a human?

A. No, no.

Q. Can you agree that you told your colleagues that the pharmaceutical release profiles of the two polymorphs would be almost identical?

A. So can you please maybe split it up.

Q. Sure. In the course of the project you wrote certain things to your colleagues, do you recall that?

A. What you mean.

Q. Reports?

A. Do you have any particular document that I should look

at?

Q. I certainly do. I am just asking if you recall that you relayed specifically to your colleagues in a meeting that there is the pharmaceutical release profiles of the two polymorphs would be almost identical?

A. Sorry, I don't know what you refer to.

Q. Okay. So let me see if we can refresh your memory. This should be the other packet I handed out, DTX 1060.

A. So the one I have is DTX 900.

Q. I'm sorry. We put it in the volume of the binder to replace or that was handed out by Mr. Aly.

A. Sorry, I have two. DTX 1060.

Q. 1060.

A. I have 1056 and then 1062. I don't have it. Do you have it? I don't.

THE COURT: I don't think I have it either.

MR. SCHULER: I apologize. I have copies I thought they were going to replace them in the binder.

THE COURT: Not a problem.

MR. SCHULER: May I approach the witness?

THE COURT: Yes, definitely.

MR. SCHULER: There's another translation at 1486 but I don't think the translation is different with regard to the sentence.

THE WITNESS: So do you have the translation then

I would please to see that.
Q. 1486.
A. So in the binder from yesterday.
MR. GLANDORF: No, from today in the second binder this volume two, plaintiffs 1486.
A. The English version.
Q. I will just walk up a copy of 1486 that your Counsel wanted you to look at.
MR. SCHULER: Is that okay?
MR. GLANDORF: Yes.
THE COURT: What is the English, 1060?
MR. SCHULER: They are both English.
THE COURT: Did you say that you have an extra copy of it?
MR. SCHULER: I will in one minute.
THE COURT: But again it's in English.
THE WITNESS: I need the German one please. Excuse me, I have now three English versions.
Q. Yes. He just asked me to hand up to you the competing translation that they have. That's all?
THE COURT: He has three English versions and no German.
THE WITNESS: But no German version or at least I haven't found it.
Q. I will ask you about the English version.

A. No, please I would like to have the German version.

MR. SCHULER: My concern, your Honor, is I don't want him translating on the fly.

THE COURT: Why don't you proceed however you would like to proceed. But, if he has to actually refer back and read the document, I think you are going to have to give him the German version.

Q. Can we agree that this lists you as an attendee at the meeting of September 27, 2001?

A. It's protocol note, and yeah.

Q. And the very first sentence of this document says that Dr. Gruss initially gave a general overview of the basics of polymorphism and pseudo polymorphism.

Do you see that?

A. I see that.

Q. And then it continues, the paragraph goes on and I just want to focus on the last sentence and it says the pharmaceutical release profiles from Tapentadol hydrochloride formulations are almost identical for both forms.

Do you see that?

A. I see that sentence.

Q. Now, does that refresh your memory as to what you discussed with your colleagues?

A. So, that was a meeting in 2001 and Jorg Holenz wrote that protocol memorandum. And to my knowledge she was contact

to clinical. And I'm not involved in her release profile determinations and that stuff.

So that probably was written by Holenz. I can't remember exactly what was discussed at that point in time at the meeting.

Q. I want to talk briefly about the FDA guidance that we discussed earlier which is DTX 910 which should have been one of the other three documents that you were handed.

Do you see that this particular guidance was issued in February of 1987?

A. So, it's a guideline, I don't, I see the date but I don't see that I have seen this document before.

Q. Okay. Let's turn to Page 38 of the exhibit and see if you remember some of the text. There's a paragraph in the middle that begins Appropriate analytical procedures, and the full sentence actually is Appropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.

Is that language you recall from FDA guidance?

A. I don't have the guidance in place here. And also all I really, to make sure that is the same writing, I need to compare with the guidance. As I said before, no, this is the guidance document the FDA usually I have seen them was a different -- I don't know, maybe I'm confused.

Is this guidance documented FDA guidance on

polymorphism?

Q. The title I have is Guideline for submitting supporting documentation in drug applications for the manufacture of drug substances.

A. Sorry, I was not involved in the drug applications and filing drug applications. So that is not a document -- did I refer to as the FDA document, not the FDA guidance document. I meant was there an FDA guidance document with respect to polymorphism.

Q. This is that. To my knowledge, this is that document, sir.

A. To my knowledge, it is not. So at least all the versions I had looked very different.

Q. Okay.

A. And then yeah. No, I think I'm not sure but I think this draft document from the FDA was not from February '87. It was far later, to my understanding.

Q. Fair enough. I just want to ask you, you testified on direct -- some of the techniques here you testified about on direct examination, correct?

A. What you mean was I testified? So, they are applied, the general techniques used for polymorphism studies.

Q. X-ray, do you see x-ray powder diffraction?

A. Yes.

Q. And Number 6 is comparative intrinsic dissolution rate.

Do you see that?

A. Yes.

Q. That is one of the techniques you used in the patent application?

A. I didn't use that.

Q. But you had the data generated for you?

A. Sorry.

Q. You had data generated for you in connection with your patent application on clarithromycin?

A. I didn't have the data. As I stated, I can't remember that I had that data.

Q. Right there on Page 47 and 48 the second sentence says It is the applicant's responsibility to collect the methods used to provide evidence concerning polymorphism and if bioavailability is affected, to provide and demonstrate the suitability of the specifications and tests for the control of the solid state form of the drug substance.

Do you see that?

A. I see that written there.

Q. Okay. Now, it is true we can agree that there is no need to control for the solid state form of Tapentadol hydrochloride, correct?

A. From my perspective there is a need to control that.

Q. What is it?

A. Sorry, as I stated also as far as you showed me --

Q. Let me rephrase. With regard to bioavailability, can we agree there is no need to control Tapentadol hydrochloride?

A. I am not responsible for this application so I can't tell you if it's required or not because I am not familiar with that. So from my perspective it is necessary to control that. But, and that wasn't one of my initials, always to provide a better understanding and that polymorphism and solid state should be considered.

Q. Understood. But, I'm saying the FDA's concern they're expressing here is whether or not bioavailability is impacted. Do you see that?

A. I cannot comment on that.

Q. You have no comment either way as to whether polymorph a or polymorph B impacts the bioavailability of Tapentadol?

A. I did not do the bioavailability studies so my field was the polymorphism studies.

MR. SCHULER: I have no further questions.

THE COURT: Thank you. Anyone else from the defendants?

MR.FITZPATRICK: Nothing further of this witness from Actavis, your Honor.

THE COURT: All right. We're done on the defendant's side.

Do you want to do a redirect?

MR. GLANDORF: Just a couple of quick questions.

THE COURT: You know what, we are going to be taking a break. Do you want to take it now or after?

MR. GLANDORF: I think we can get through this.

REDIRECT EXAMINATION BY MR. GLANDORF:

Q. I just have two documents I'm going to be referring to. I have printouts of one here.

MR. GLANDORF: May I approach the witness and the Court?

THE COURT: Yes. Any issue with the exhibits? Anyone?

MR. ALY: No.

THE COURT: No. All right. Any demonstratives? Nothing else?

MR. GLANDORF: Nothing else.

THE COURT: Go ahead.

Q. Can you, Rob, can we pull up plaintiff's Exhibit 507?

Dr. Gruss, do you recall counsel for Alkem asking you about the role of impurities with respect to Tapentadol hydrochloride?

A. Yes.

Q. Now, have you seen this table in plaintiff's Exhibit 507 previously?

A. Yes.

Q. What is shown here?

A. It shows a list of batches and on the left side they

are the batch names and the form, the crystalline form and on the right side. There is a list of the impurities in that batch or samples of that batch.

Q. You are referring to the left most column and the right most column. Is that right?

A. That's correct.

Q. The left most column you said that they have the batch and then the polymorphic form.

Is that right?

A. Right. It's the batch name and the polymorphic form in brackets after that.

Q. In the right most column, what is shown there?

A. There is impurities shown and the yeah the amounts of impurities in that batch.

Q. Let's show now, Rob, the next page as well if we can turn to the next page, doctor, 63011.

A. Yes the same, on the left side batch names and crystalline forms after the batch in brackets and on the right side impurities in both of the rows.

Q. And the third page as well?

A. The third page, on the left side, sorry, sir, my page is different.

Q. My copy is missing a page.

A. The 012 is missing in my copy.

THE COURT: Same here.

Q. Let's come back to this document in a minute.

THE COURT: I think it's also missing 14 as well. Right?

THE WITNESS: Yes.

Q. We will come back to the document in a minute. Let's go to the other exhibit, plaintiff's Exhibit 553.

Doctor, do you recall Counsel for Alkem asking you about the work that was done by Crystallics?

A. Yes.

Q. And do you see your name here on the cover of this document?

A. Yes.

Q. And if we could turn to Page 2, 74877?

A. I don't have the batch numbers here but I have Page 2. Yeah, I have it.

Q. Do you see there's a reference here to Crystallics and to Grunenthal?

A. Below, yeah, Crystallics and Grunenthal.

Q. And if you refer to the first sentence it's talking about a crystallization process optimization study of CG 5503?

A. Yes.

Q. And there's a reference to 97 crystallizations. Do you see that?

A. I see that.

Q. Is this the same study that counsel for Alkem was

asking you about?

A. I assume so, yes.

Q. I'm sorry, if we could go back to the first page again. What is the date on this document?

A. Twelfth of May, 2003.

Q. Let's turn now to Page 74898.

A. Can you tell me the other page numbers?

Q. Sure. It's 23. Would you read for the Court the first bullet point there?

A. High levels of impurities GRT 4045Y and GRT 0912Y were observed to have no effect on the polymorphic form outcome in Step 3.

Q. Let's turn to the next page as well which is 899 which is Page 24 of the PDF. And you see there is, there's two heading. The first two headings are here is Crystallics experience and Grunenthal experience?

A. Yes.

Q. Will you read the Crystallics experience bullet point for us?

A. I see that.

Q. Would you read it for us?

A. The impurities GRT 4045Y and GRT 0912Y have no effect on the polymorphic form outcome.

Q. And what does that say for the Grunenthal experience?

A. The Grunenthal experience. At that point in time a

sufficient amount of GRT 0912Y stabilizes the polymorphic form B for a period of hours/days/months.

Q. What is your understanding of the role that impurities have in the polymorph form of Tapentadol hydrochloride?

A. So for me it indicates the impact of the impurities is not yet fully understood because they have two different opinions or experiences at that point in time.

Q. That is what this document indicates?

A. Yes. To me, yes.

Q. Is that your recollection of Grunenthal's understanding in 2003?

A. As far as I remember, yes.

Q. Do you recall seeing data for examples of form A that had impurities in them?

A. Yes.

MR. GLANDORF: No further questions.

THE COURT: All right. Thank you very much.

MR. ALY: Your Honor, it did raise a couple of questions but I don't know if I may be allowed to recross.

THE COURT: Just do it very briefly. Go ahead. If there's anything further I'm going to allow the plaintiff as well.

MR. ALY: It's only to read the rest of the slide actually.

THE COURT: Okay. Go ahead.

RECROSS EXAMINATION BY MR. ALY:

Q. PTX 553 at 24. Dr. Gruss, you read the first two parts of this. I just want to explain there's also a third bullet point with the possible explanation, correct?

A. That says possible explanation. I referred to that at that point in time.

Q. And that understanding is that Crystallics had conducted well controlled cooling experiments from solution, they had done a good experiment, correct?

A. That's what was said. So at least the experiment, the cooling experiment has been well controlled. And this well controlled refers, I have to explain that, to the equipment they used because they had machines we didn't have at that point in time.

Q. The way Grunenthal did the experiment, the form B they got because it was evaporating the solvent until dryness, correct?

A. It was a different approach to the crystallization. As I mentioned before, this is big space, you have to investigate.

Q. It was not well controlled, correct?

A. No.

MR. ALY: Thank you.

THE COURT: Anything else from the plaintiffs?

MR. GLANDORF: Can I ask him to clarify that last statement?

THE COURT: Yes, go right ahead.

FURTHER REDIRECT EXAMINATION BY MR. GLANDORF:

Q. He asked you on the second point, he said it was not well controlled, what is your answer to that?

A. So it would mean it has been well controlled. So as I stated well controlled refers to the equipment they had. Like they had ultimate conduct reactors where they could really steer the temperature for the cooling profile, that you get really good controlled conditions. And they have a great experiment.

Grunenthal, to my knowledge, has a different machine. And they also control the pressure under which so there has been measure instruments adjusted to that equipment and that could control the pressure and the conditions. So the solid can be, yeah, evaporated and the heat. So that the equipment is also controlled. It's a different type of experiment.

THE COURT: Okay.

MR. GLANDORF: Thank you.

THE COURT: Anything else? Thank you.

Mr. Schuler.

MR. SCHULER: No I'm anticipating we are taking a break.

THE COURT: We are taking a break. We are done with the witness. Thank you very much, doctor. Much appreciate your time on this. You are excused.

We are going to take a five-minute break and we are starting with, who's the next witness.

MR. KOTE: Juergen Haeussler.

THE COURT: All right. Thank you very much.

(Whereupon a short recess was taken.)

THE COURT: Plaintiffs should call their next witness, please.

MR. KOTE: Juergen Haeussler.

THE COURT: Hello, sir. Come forward. We will have you sworn.

J U E R G E N H A E U S S L E R, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. KOTE:

THE COURT: Good morning. Thank you. Did we exchange the exhibits for this witness?

MR. KOTE: I'm sorry, the binders.

THE COURT: Tell me when you folks are done taking a look at the exhibits.

MR.FITZPATRICK: Just a moment, your Honor.

THE COURT: Yes.

MR. SCHULER: I don't have a problem with them but the cover, the index talks about approval. I don't see an approval letter. 695.

THE COURT: Take a look.

MR. KOTE: I think that's a title issue 695 is

describing.

MR. SCHULER: That is what you want.

MR. KOTE: I think it's just probably a mislabel.

THE COURT: So we are okay with the exhibits?

MR. SCHULER: Yes, your Honor.

THE COURT: All right. They are all fine. Let us begin.

Q. Good morning. Could you please state your name for the record?

A. My name is Juergen Haeussler.

Q. Can you please briefly describe for us your educational history?

A. After high school I went to medical school in Germany and graduated there. And then I went on to clinical training in anesthesiology and in intensive care in Germany and the U.K.

Q. Where did you work Dr. Haeussler?

A. I am working at Johnson & Johnson at the pharmaceutical affiliate with is called Janssen.

Q. How long have you been working at Janssen?

A. For about 16 years.

Q. What is your position at Janssen?

A. I'm the vice-president for pain and schizophrenia development.

Q. Can you briefly describe your job responsibilities at Janssen?

A. I'm heading up a group of scientists and physicians who are in charge of designing, conducting and reporting clinical trials that are being used for submissions to health authorities, including FDA, with the intention to get a new chemical entity approved.

Q. Have you held any other positions at Janssen before your current position?

A. Yes, I started off as medical leader for pain and I've slowly got increasing responsibility.

Q. For all together how many years experience do you have in development of pain medications?

A. About 16 years.

Q. Can we have PTX 1555, please.

Do you recognize this document?

A. Yes.

Q. What is it?

A. It's the clinical overview document as part of our submission referring to Tapentadol immediate release in the treatment of moderate to severe acute pain.

Q. Your submission to whom?

A. To various health authorities but including FDA.

Q. Did you have any responsibilities with respect to this submission?

A. Yes, I'm part of the group of senior managers who review and provide the final sign off of the document before it

gets shipped out to health authorities.

Q. Can we please go to Bates number JN 0319284 and also 285. I would like to get blown up the bottom of the paragraph at the bottom of 284 and spans over to 285.

Those paragraphs now that is blown up is under the section labeled Relevant Scientific Background. And you can see there it states in the first sentence, Current opioid analgesic therapy is complicated by their side effect profile especially in the gastrointestinal and central nervous systems. Do you see that?

A. Yes.

Q. Can you explain in general terms what that means?

A. Opioids have a very powerful effect on pain relief and sometimes unneeded. The problem is many patients don't tolerate opioids for more than a few days because of side effects, which means complaints that they develop what's stated here, gastrointestinal side effects of the first two, nausea and constipation seen as side effects refer to things such as dizziness, drowsiness, etc.

Q. The paragraph goes on to say Unlike pure MU opioids, Tapentadol acts via two pathways for analgesia that together can provide advantages compared to either mechanism alone.

Do you have an understanding what that means?

A. Yes.

Q. Can you please describe for us generally?

A. Tapentadol is a molecule with two mechanisms of action which means that it acts in two different, in two different ways on different parts of the body.

And both of these mechanisms act together to achieve pain relief.

So, in order to achieve the same degree of pain relief the amount of opioid, the amount of action on the opioid mechanism can be reduced which means that the opioid related side effects can also be reduced.

Q. The next sentence I'm going to read, I'm going to skip the portion that's in the parenthesis, says Tapentadol IR provides analgesia similar to the pure classical MU opioid analgesic Oxycodone IR at doses of ten milligrams and 15 milligrams with an improved gastrointestinal tolerability profile and a similar central nervous system tolerability profile compared to Oxycodone IR.

Do you see that?

A. Yes.

Q. This sentence immediately follows the sentence before it regarding these mechanisms of action.

Can you tell me, is there some connection between those two things?

A. Yes, opioids cause side effects which are listed here nausea, vomiting, and are also seen as side effects as well as constipation. And the second mechanism of action provides part

of, one part of the analgesic benefit means the opioid mechanism only needs to provide another part and not the entire benefit. In laymen's terms the opioid load can be reduced for the same degree of pain relief.

Q. What do you base that statement on?

A. This is really based starting from a series of very comprehensive pre-clinical experiments which in effect got us interested in the molecule to begin with. And then it led to predictions about how these products would behave in a clinical setting. And this is exactly what we found.

Q. So, excluding Tapentadol, are you aware of any other opioids that have these two mechanisms of action in a single molecule?

A. I'm not.

Q. The paragraph goes on to say, This is a significant benefit compared to current opioids therapies abused because adverse events often limit therapy with opioids for the relief of moderate to severe pain.

Do you agree with that statement?

A. Yes.

Q. Why do you agree?

A. Because side effects can sometimes become so bothersome that patients have to discontinue their opioid treatment, even though they would benefit, continue to benefit from them in terms of the pain relief that they experience.

This is not, this is not just new patients. In studies that are conducted over more than a few days, up to half or even more than half of these patients will have to discontinue these treatments.

Q. Let's go on to PTX 1551, please.

Dr. Haeussler, do you recognize this document?

A. Yes.

Q. What is it?

A. It's the clinical overview document for the Tapentadol extended release formulation in the management of moderate to severe chronic pain.

Q. So the first one we looked at was immediate release?

A. Immediate release and acute, and this is extended release and chronic.

Q. And do you have any responsibilities or did you have any responsibilities with respect to this submission?

A. Yes.

Q. What were they?

A. Like before I'm part of the senior management group who review and sign off, provide the final sign off of these documents before they get submitted.

Q. Before we go a little deeper into this document, let me ask you, when did you first interface with the FDA regarding Tapentadol ER?

A. On the ER formulation we had the first meeting in 2005,

I believe it was in August, which was called so called interface two meeting.

Q. What was the purpose of that meeting?

A. Interface two meeting means that we engage in a discussion with the agency on the specific data requirements that the agency would need to be able to decide upon approving or not approving a product for a condition for an indication that's desired by the sponsor.

Q. And at that time did Janssen express any interest in any particular indications?

A. Yes, we started off with a discussion on the management of chronic moderate to severe pain. And then we continued to also discuss a specific indication for diabetic peripheral neuropathic pain.

Q. Can you explain briefly what diabetic peripheral neuropathic pain is?

A. This is a pain that arises from a condition which sometimes or many times happens in diabetes. Diabetes causes a lot of tissue damage to many tissues, but it also effects the nerves in the body. And that's why it's called peripheral polyneuropathic.

Q. What do the words "peripheral neuropathy" mean? I am a little confused about it. Can you explain it a little more?

A. The nervous system is divided into two parts, the central nervous system and the peripheral nervous system. The

central nervous system being the brain and the spinal cord. And the peripheral nervous system, all the other nerves and receptors in the body.

Q. Is diabetic peripheral neuropathy a type of nociceptive pain or a neuropathic pain?

MR.FITZPATRICK: Objection, your Honor. So, as best as I can tell, this witness is offering expert testimony. He is not been offered as an expert. We got no report from him. He is not an inventor of any of the patents in suit.

THE COURT: I would imagine he should be able to have some responses as a fact witness and he can go ahead with respect to that.

MR.FITZPATRICK: Very well.

THE COURT: Thank you. And if you can clarify the question, that would be helpful.

Q. Sure. So, this submission I believe you testified -- let me backup.

I believe you said before that you went to the FDA and talked about indications that you were interested in getting?

A. Correct.

Q. One of those had to do with neuropathic pain associated with diabetic peripheral neuropathy. Is that correct?

A. That's correct.

Q. I just want to understand, diabetic peripheral neuropathy is a neuropathic or nociceptive pain?

A. This is clearly a neuropathic pain.

Q. And you said something before about neuropathic pain going to either the central nervous system and/or the peripheral nervous system.

What does the peripheral portion mean?

A. It means the nerves in the body outside of the brain and the spinal cord, pretty much elsewhere else.

Q. Is more than one nerve being effected by DPN?

A. Yes, all the nerves. That's why it's also called polyneuropathy.

Q. Did the FDA provide Janssen with any guidance regarding what it needed to do in order to obtain approval for those two indications you were interested in?

A. Yes. We received very specific items regarding the first indication. We were told that we have to study two conditions which are clinically relevant and have to provide -- at least two conditions and have to provide positive studies based on FDA's determination, not the sponsor's determination, on two different of these conditions regarding the diabetic polyneuropathy.

We started off by asking the agency whether one of these two required conditions could actually be a neuropathic pain model. And we offered up the DPN study, the DPN model. And the FDA agreed with us that one of these two could be the DPN model.

And then we continued with asking what would be required in addition for the second indication. And the FDA's response was that like for any specific indication, they required replicative evidence which means that two positive studies are required in the same condition specifically to get that specific indication label.

Q. Does this submission to the FDA, PTX 1551, report any clinical studies relating to the efficacy of Tapentadol ER with respect to moderate to severe chronic pain?

A. Yes.

Q. Can we pull up JN Nucynta 74680? Highlight the last portion at the bottom.

Q. What chronic pain conditions were studied in this submission?

A. We studied the following conditions: Chronic low back pain, lower back pain, chronic painful osteoarthritis which means O.A. in this document, and also full diabetic peripheral neuropathy.

Q. And do any of these three chronic pain conditions have neuropathic pain components?

A. The DPN very clearly is related to neuropathic pain which means pain due to nerve damage. The low back pain indication has neuropathic components to a variable degree. It's many times it's very difficult in patients to decide whether or not in a specific patient there is neuropathic pain

present.

Q. So, you said that for chronic lower back pain that neuropathic component is variable degrees in terms of how much it effects a particular patient, correct?

A. Yes.

Q. Did Janssen exclude from the lower chronic back pain study patients who showed symptoms of neuropathic pain?

A. We excluded patients for whom there is a very clear specific reason for their pain. But, in most patient studies, say up to 90 percent, there is no specific reason. It can be ascertained that sometimes the clinical pictures look very much like a neuropathic component.

Q. Could we please have Bates number JN Nucynta 0074683 and section 4.4 and 4.31, please?

So, why were these three chronic pain conditions that were submitted selected for this submission?

A. This was really based on FDA guidance. So we have to choose pain conditions that are really relevant which means that usually physicians encounter, and where the questions does comes up, whether the pain is sufficiently severe and not treated well enough by others means to warrant an opioid therapy. And so these are just the three most common conditions that we use.

Q. Okay. Can we go back please to JN Nucynta 0074680? Again the bottom portion if you'd highlight it.

Right in the middle of this bullet here under Section 4, there's reference PAI 3015/KF36 and then the parenthetical painful DPN.

Do you see that?

A. Yes.

Q. Do you understand what was that a reference to?

A. Yes. This refers to the first of the two DPN studies we conducted.

Q. Can I have PTX 727 please, Rob?

Dr. Haeussler, do you recognize this document?

A. Yes, I do.

Q. And what is it?

A. It's the clinical study report of the 3015 study, the first DPN study we conducted.

Q. Did you have any job responsibilities in connection with this study?

A. Yes, I'm part of the senior management team who provides the final sign off for this document.

Q. And there is a reference here to PAI 3015. Do you see that?

A. Yes.

Q. Is this the same study that was identified in the submission?

A. Yes.

Q. Let's go to the last page of PTX 727, please, and Bates

number ending in Bates number 542 and the conclusion.

Did the PAI 3015 study draw any conclusions regarding the efficacy of Tapentadol ER with respect to diabetic peripheral neuropathy?

A. Yes. The study concluded that the Tapentadol was actually effective, was an effective pain medication for this condition and that the results were robust, which means that all the measures go in the same direction

Q. Let's go on to PTX 1499, please, Rob.

Can you highlight this portion that goes down to indications and usage all the way to the top?

Dr. Haeussler, do you recognize this document?

A. Yes.

Q. What is it?

A. It's the highlighted portion of the prescribing information for Tapentadol ER also called the label.

Q. Is it just the highlight that's considered the label?

A. No, the entire document which is very lengthy.

Q. So, this exhibit PTX 1499 is almost forty pages long. So, the entirety of that is the label?

A. The entire, yes, the entire document is the label.

Q. And is this document PTX 1499 something that you reviewed in the normal course of your job responsibilities at Janssen?

A. Yes.

Q. What was your involvement with this?

A. At the time of initial approval we engaged in a discussion with FDA to set a standard process which is called label negotiations. And I was part of the sponsor team during these negotiations.

Q. Okay. So now we have been talking primarily about Tapentadol. And you mentioned this, the label for Nucynta ER. Is there a difference, sir?

A. Yes. Tapentadol is the molecule and Nucynta ER is the extended release formation and brand name.

Q. For what indication of use -- actually, can we also pull up the date on this, PTX 1499? This shows it was last revised in August of 2011.

Do you see that?

A. Yes.

Q. So, what indications of use was Nucynta ER approved for as of August 2011?

A. For the management of moderate to severe chronic pain in adults when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

Q. Can we go to JN Nucynta 0273457?

Was this label supported by any clinical studies?

A. Yes, it was supported by four studies that are mentioned here in different clinical chronic pain conditions.

Q. I'm sorry, which studies was it supported by again?

A. The label specifically was supported on two of these four submitted studies. And the reason was that these are the only two studies that FDA determined positive and sufficient for inclusion in the label.

Q. Can we go to JN Nucynta 0273458? Let's get this portion down here.

Does the label provide any details about the DPN study that you mentioned?

A. Yes, it specifies the study design, the dosing and also the results, are most important results of the study.

Q. There's a reference here again of a paragraph to the DPN study.

Do you know which DPN study that refers to?

A. Yes, it's the 3015 study because this is the only DPN study in that submission.

Q. Let's go back to the first page of PTX 1499, please. So again the indications and usage here at the bottom, did the treatment of diabetic peripheral neuropathy fall within the chronic pain indication that's shown here in the front of PTX 1499?

MR. SCHULER: Objection, your Honor, that's clearly phrased as calling for expert testimony. I'll also note that this witness was disclosed in Rule 26 disclosures that had nothing whatsoever to say about that subject, which I'm happy to address as well. That's the reason we didn't

depose this witness because he was literally only disclosed as quote development of Nucynta at Janssen.

THE COURT: All right. So rephrase the question please.

Q. Doctor Haeussler, do you have experience working with the FDA with respect to this document? Is that what you were telling me before?

A. Yes, I do.

Q. Based on your interactions with the FDA, do you have an understanding as to whether or not the treatment of DPN falls within indications and usages shown here?

MR. SCHULER: Same objection, your Honor. It's clearly outside the scope of what they presented in the report. It's also --

THE COURT: I'm going to allow it at this point. As I said before, it's a bench trial. I'm going to take it and I'm going to weigh it. But, to the extent he is here as a fact witness, correct? Correct, he is being offered as a fact witness?

MR. KOTE: Yes.

THE COURT: He has had involvement in terms of the FDA. You're going to lay a foundation with respect to that. To the extent you have anything, obviously you can go through it on cross. And if he's anything beyond what you just stated, raise it again and we will address it, Counsel.

MR.FITZPATRICK: I just want to state a hearsay objection too, your Honor, because clearly the question calls for hearsay testimony about what he understood from the FDA.

THE COURT: All right. I'm going to allow it at this point. But, I want a foundation laid. I understand he has had interactions with the FDA. Get precisely at his background and his knowledge so that he can answer these questions appropriately.

And then again to the extent you have any issue with it, you may go through it on cross. Understood? Thank you.

Q. PTX 1499 which you describe as the label, do you provide -- excuse me. Strike that.

Does the FDA dictate to Janssen exactly what's going to be included within the label?

A. Well, it's an FDA document so they have the final say.

Q. Does Janssen have any say in what may be in the label?

A. Well, there are always degrees of some areas of disagreement and they are being negotiated. That's why we have label negotiations.

Q. Are you involved at all in negotiations -- were you involved at all in negotiations of this label with the FDA?

A. Yes, I was.

Q. Based on your interactions with the FDA with respect to this label, do you have an understanding as to whether DPN is

covered under this indication of use?

A. Yes.

Q. What is your understanding?

A. Well, this is just following directly the guiding step that you receive from the FDA which means that we have to provide two studies for an approval. And one of these two studies can be the DPN study. And as it turned out, it's FDA's written statement that one of these two studies is the DPN study.

Q. And is this the only label that you've had interactions with the FDA about?

A. No.

Q. And do you have discussions with the FDA regarding clinical studies and what goes on the label?

A. Yes.

Q. Do you have an understanding as to whether, when a clinical study is included on a label, it is part of the indications and usage that were identified on the label?

A. Yes.

Q. What's your understanding?

A. Well, if a study is specifically mentioned in a label, then that study is clearly part of the label indication.

Q. Okay. In your experience working with the FDA on submissions about new products and talking about labels, are you aware of any situation where a label, excuse me, where a

study has been used to support an indication for use where that indication for use was found to not cover the study itself?

MR. SCHULER: I'll object, your Honor. First of all, I don't understand the question.

THE COURT: I'm not sure I understand the question either.

MR. KOTE: Strike that. I will come back to it later.

THE COURT: Thank you.

Q. So, just briefly, what are your bases for believing that the treatment of DPN was on label for this indication for use in PTX 1499?

A. The DPN study 3015 is specifically stated in the label and quoted there as one of the two studies.

Q. In addition to this indication for moderate to severe chronic pain, PTX 1499, did Janssen pursue any additional indication for treatment regarding neuropathic pain associated with DPN for Nucynta ER?

A. Yes.

Q. Did Janssen do so in this submission that we talked about awhile ago?

A. I'm sorry, can you repeat the question?

Q. Let me backup. Can we pull up again real quickly, PTX 1551?

In addition to the indication for moderate to severe

chronic pain that we saw on the label PTX 1499, did Janssen pursue an indication for the treatment of neuropathic pain associated for, associated with DPN in this particular submission?

A. Not in this submission.

Q. Did Janssen do so in another submission?

A. Yes.

Q. So, if the treatment of neuropathic pain associated with DPN was already on label with respect to Nucynta ER as of August 2011, why did Janssen pursue a separate indication for the treatment of diabetic peripheral neuropathy?

A. I'm not a specific expert on marketing and promotion but it's been my understanding that in order to get a very specific indication into the label, which means being promotable, the FDA requirements for replicative evidence in this condition have to be met, which is exactly in line with what we were told at the end of these two meetings.

Q. Did you believe at the time that Janssen needed to have a separate indication for neuropathic pain associated with DPN in order for the treatment of DPN to be on label with respect to the August 2011 version of the label which was PTX 1499?

A. No.

Q. Can I have PTX 732, please?

Dr. Haeussler, do you recognize this document?

A. Yes, I do.

Q. What is it?
A. It's the clinical study report for the second DPN study we conducted.
Q. And do you have any experience with this study from your work at Janssen?
A. Yes.
Q. What is your experience?
A. I signed off as one of the people who signed off on the final study report.
Q. How, if at all, is this study different than the study that was done before, PAI 3015?
A. Those studies are virtually identical.
Q. Why did you run a second study?
A. This was direct following of FDA guidance about producing replicative evidence for, which means evidence in two studies in the same condition to be able to get that specific indication in the label.
Q. Can I have PTX 695? Do you recognize this document?
A. Yes, I do.
Q. What is it?
A. It's a part of the prescribing information for Nucynta ER updated with the second indication.
Q. Okay. Can you pull up the date again for me, Rob?.
And it shows the date of 9/2013. Do you see that?
A. Yes.

Q. So, is that consistent with your understanding of when this label was in effect?
A. Yes.
Q. And is this label something that you had experience with from your time at Janssen?
A. Yes.
Q. Again, what was your experience in connection with this label?
A. I was part of the label negotiating team, even though there was not much negotiating on this.
Q. Okay. For what indications of use was Nucynta ER approved on this label?
A. First for the original indication, moderate to severe chronic pain in adults and with all kinds of other stipulations. And then the second indication, neuropathic pain associated with diabetic peripheral neuropathy in adults.
Q. Let's go to PTX 1383. Do you recognize this document?
A. Yes, I do.
Q. What is it?
A. It's the updated prescribing information updated 2014.
Q. Do you have an understanding of what the reason was for the update?
A. This was something we were told from FDA. And the explanation we were given was this is part of FDA's effort to harmonize all of their opioid labels.

Q. So, can we pull out both PTX 695 and 1383 and focus on just indication and use, please?

So, the first indication for use in the PTX 695 which is the 2013 version reads moderate to severe chronic pain in adults and it continues on, when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

Did I get that right?

A. Yes.

Q. And the first indication for use in the current version of the label PTX 1383 says pain severe enough to require daily around-the-clock long term opioid treatment and for which alternative treatment options are inadequate.

Did I get that right?

A. Yes.

Q. Okay. Is there a difference in the studies that were used to support the first indication in the 2013 version of the label versus the 2014 version of the label that is now the current label?

A. We did not submit any other data, so, it would be the same data.

Q. And again why did the wording change?

A. What we understood from the agency communication was that this was an effort which effected all opioids and it was related to the agency's efforts to insure that there was harmonization across opioid labels.

Q. Can we go back to just 1383 again, please? Highlight, once again, the indications for usage. Let's focus in on the first indication.

Based on your experience, does the first indication of the current version of the Nucynta ER label cover the treatment of neuropathic pain associated with diabetic peripheral neuropathy?

A. Yes.

Q. Would your answer be the same if this label did not include the second indication for diabetic peripheral neuropathy?

A. Yes.

Q. Would your answer be the same if this label removed every reference in it to diabetic peripheral neuropathy?

MR. SCHULER: I'm going to object, your Honor. That's for expert testimony. It's an incomplete hypothetical.

THE COURT: I agree with that. That is sustained. You can rephrase that question.

Q. How many studies, if you can remind me, Dr. Haeussler, were required to gain this first indication?

A. Two positive studies by FDA standards.

Q. Okay. Is it your understanding that you could have gained approval of this first indication with only one study?

A. No, that goes against what we were told.

MR. KOTE: No further questions.

THE COURT: Thank you very much. Let's turn to the cross. Who's doing this?

MR.FITZPATRICK: Your Honor, me. May I just have a moment to confer with Mr. Capuano?

THE COURT: Yes.

MR.FITZPATRICK: I will just be a moment.

(Whereupon there was an off-the-record discussion)

MR.FITZPATRICK: May I proceed, your Honor?

THE COURT: Yes. Go right ahead.

CROSS EXAMINATION BY MR. FITZPATRICK:

Q. Good morning, Dr. Haeussler.

A. Good morning.

Q. My name is Tony Fitzpatrick and I represent Actavis. I'm going to be asking you a few questions.

Mr. Haw, if you would please pull up PTX 1383. And if you could, actually if you could highlight the indications and usage section there. Thank you.

Doctor, if I understand your direct testimony correctly, this is the current label for Nucynta ER, correct?

A. The one that's dated yeah 2014. That's my understanding, yes.

Q. And so this is the one with the two indications, correct?

A. Yes.

Q. The severe pain indication. You will understand what I

mean if I refer to it as that?

A. Yes.

Q. And the DPN indication, correct?

A. Yes.

Q. If I refer to the DPN indication, you will know what I'm referring to, right?

A. Yes.

Q. And the word "neuropathic" does not appear in the first indication, right?

A. That's correct.

Q. And the word "polyneuropathic" does not appear in the first indication, correct?

A. That's correct.

Q. And you testified that in fact the FDA approved the first indication based on the low back pain study, right?

A. That's one of the two studies, yes.

Q. And the DPN, one study, right?

A. That's correct.

Q. So, if I refer to the DPN one study, you understand I'm referring to the first diabetic peripheral neuropathy study that was conducted, right?

A. That's correct.

Q. Thank you. So, those two studies, the low back pain study and the DPN one study were not considered sufficient to get approval for the second indication, right?

A. Correct.

Q. Janssen had to conduct the DPN two study to get approval for the second indication, right?

A. Correct.

Q. And there's no data in the low back pain study about neuropathic or polyneuropathic pain, right?

A. Yes, not specifically stated, yeah.

Q. In fact, the subjects in the low back pain study were not screened to determine whether or not they had low back pain caused by some polyneuropathy, correct?

A. Yes.

Q. And it was understood in the literature in fact that further research would be required in order to conclude as to whether Tapentadol would be effective in patients with low back pain with the neuropathic components, correct?

A. I actually don't recall that.

Q. You don't recall that?

A. No.

MR. FITZPATRICK: I should have handed out exhibits, your Honor, and I apologize.

THE COURT: Go ahead. Is it just one packet?

MR.FITZPATRICK: It's just one packet.

THE COURT: Any issues with the exhibits?

MR. KOTE: Assuming Counsel can show a foundation for him testifying, no objection.

THE COURT: Thank you.

Q. Doctor, I think that the first document in that binder which is DTX 1660 --

A. Yes.

Q. -- should be a paper from the Journal, expert opinion on pharmacotherapy from June of 2010. Do you see that? Are you familiar with that paper?

A. Actually, yes, I am.

Q. This is a paper that was authored by a number of your colleagues at Johnson & Johnson, correct?

A. Yes.

Q. And this relates to the initial, the original low back pain study, right?

A. Yes.

Q. And this was published in June of 2010. Was that correct?

A. Yes, that's what it states.

Q. And this is the study in which patients were not screened for whether or not their pain had any neuropathic component, correct?

A. I would have to reread it because this is a long time ago.

Q. But, your understanding, as you indicated just a few moments ago, was that in that initial low back pain study, patients were not screened for neuropathy, correct?

A. Yes. But just to clarify that in my recollection we did, we excluded patients for which, for whom there is a clear specific anatomical abnormality, for example, a herniated disc that is commensurate with symptomatology. Those patients were excluded. But, not patients who may have otherwise neuropathic pain components, yes.

Q. Then if you turn to the next document in the binder, DTX 1664, that's a paper from the Journal of Pain Research published in 2011.

Do you recognize that paper?

A. Yes. I'm not sure I have read it before, but I see it here.

Q. You don't know whether you've read this paper previously?

A. I have read so many papers.

Q. The title of this paper is Tapentadol In The Management of Chronic Low Back Pain: A novel approach to a complex condition.

Do you see that?

A. Yes.

Q. If I can ask you to turn to Page 206 using the page numbers in the bottom left-hand corner, and there's a heading there Tapentadol: Clinical trials in chronic LBP.

Do you see that?

A. Yes.

Q. That's referring to chronic low back pain?
A. Yes.
Q. And it speaks about Tapentadol having been the subject of an extensive testing program.
Do you see that?
A. Yes, it was expensive too.
Q. And in the second sentence it indicates that chronic LBP was one major pain model used in the phase three clinical program and has been included in the current phase 3 program to gather further evidence on the use of Tapentadol in this prevalent chronic pain condition.
Do you see that?
A. Yes.
Q. And that's referring to the first, the original LBP, lower back pain clinical trial, correct?
A. Yes.
Q. Then if I can ask you to turn to Page 208, the conclusion is there in the bottom right-hand corner. And the last sentence on Page 208 beginning with Further research, do you see that?
A. Yes.
Q. That indicates, it reads, Further research is required, however, particularly into efficacy and safety in patients with pure neuropathic pain and to provide specific data on LBP with a neuropathic component.

Do you see that?

A. Yes.

Q. So, the authors of this study wrote and concluded that even in light of the first lower back pain study, further research was required to determine whether the product was effective in lower back pain with a neuropathic component, correct?

A. Yes. It says to provide specific data on lower back pain with a neuropathic component.

Q. Now, referring now to the DPN two study.

A. Yes.

Q. Do you have that one in mind?

A. Yes.

Q. That study excluded patients who had other types of pain, right?

A. The DPN two study?

Q. Yes.

A. I thought both of these studies that they -- both DPN studies excluded patients with other types of pain.

Q. Well, let's look at the DPN two study. It's PTX 732. This is the one that you testified about just a few minutes ago during your direct examination. This is Janssen's submission to the FDA regarding the DPN two study, correct?

A. This is the final study report, yes.

Q. If I can ask you to turn to pages 10 to 11 of this

document, and just for the record it's JN_Nucynta_0277011 to 012.

Do you see that those pages?

A. Yes.

Q. And at the bottom of Page 10 going onto the top of Page 11, it says Subjects were not to be enrolled in this study if it was determined, upon prestudy examination, that they, and then it has a list of four bullet points, four different sets of criteria for excluding people from the study, right?

A. Yes.

Q. And the second one says Had presence of conditions other than painful DPN that could confound the assessment or self-evaluation of pain, for instance, fibromyalgia, significant skin conditions such as abscesses, significant osteoarthritis, low back pain and inflammation.

Do you see that?

A. Yes.

Q. So, in the DPN two study there were specific criteria to exclude patients with low back pain, correct?

A. Yes.

Q. And to exclude patients with osteoarthritis, right?

A. Yes. Well, this is standard exclusion criteria just to insure that if you study a specific condition, you don't have a session where the patients can't decide what their pain is and what they actually improve on. So, this is every study.

I'm sure, all of our studies actually have this, have this exclusion criteria, of course tailored to the condition we are studying.

Q. Understood. But, these are the criteria for excluding people from the DPN two study, right?

A. These are some of the criteria, yes.

Q. You testified on direct examination that the FDA required Janssen to conduct the DPN two study in order to get the DPN indication on the label, correct?

A. The specific DPN indication, yes.

Q. And that was because the FDA requires replicative evidence, correct?

A. Of the same, yes, of the same specific indication, yes.

Q. And you testified that the reason that Janssen wanted that specific indication is because it wanted the product to be promotable for that indication, correct?

A. That's my understanding, yes. I am not an expert on promotion though.

Q. And promotion, and to say that it would be promotable means the ability to go to physicians and specifically promote the product for that indication, correct?

A. That's correct.

Q. That's a process known as detailing, right?

A. Yes.

Q. That's the process whereby sales reps from Janssen and now Depomed go and meet with physicians and promote the product to them, right?

A. Yes.

Q. So in order to do that, Janssen wanted to have the specific indication, the second indication from the label, wanted to have that on the label, right?

A. Yes, that's my understanding.

Q. Now, exhibit 732, I think that's the one we still have up here -- if we can go to the cover page Mr. Haw -- that's part of the Janssen's submission to the FDA, correct?

A. It's part of the second submission, yes.

Q. And it indicates -- if we can get just right down at the bottom there Mr. Haw -- right down to the bottom of the page, that's a confidential document of Janssen's right?

A. Yes.

Q. It's not a public document, correct?

A. Yes.

Q. Okay.

If we can go to, Mr. Haw, PTX 727, this is part of the submission, as I understand it, regarding the DPN one study, right?

A. Yes.

Q. And again this is a confidential document of Janssen's, correct?

A. Yes.
Q. It's not a public document?
A. This document is not public.
Q. Then if we go to PTX 1551, this document is again part of Janssen's submission to the FDA regarding the Tapentadol extended release formulation, right?
A. Yes.
Q. And again it's a confidential document, right?
A. Yes.
Q. Not a public document?
A. Correct.
Q. And then finally PTX 1555, Janssen's submission to the FDA regarding the immediate release formulation of Tapentadol, right?
A. Yes.
Q. Again a confidential Janssen document, right?
A. Yes.
Q. Not a public document?
A. This document is not public.
Q. And, doctor, you testified at the outset of your direct examination that you attended medical school in Germany, correct?
A. Yes.
Q. And that you did some training in anesthesiology and emergency medicine. Is that correct?

A. Intensive care, yes.
Q. You don't practice as a medical doctor in the United States, correct?
A. That's correct.
Q. You're not qualified or licensed as a medical doctor in the United States?
A. That's correct.
Q. Correct. You don't prescribe medications to patients in the United States?
A. That's correct.
Q. Correct. You haven't reviewed my client Actavis's labeling for its Tapentadol products, correct?
A. Correct.
Q. You haven't reviewed any of the other defendants' labels for their Tapentadol products, right?
A. Not to my knowledge, no.
Q. You don't know what they say, correct?
A. That's correct.
Q. Now, even though Tapentadol is approved to treat polyneuropathic pain, it's not a first line option for that type of pain, correct?
A. No opioids types, that's correct. But I would like to explain. Opioid type drugs have a lot of baggage and for that reason they are rightfully restricted. Therefore opioids are almost never first or second line of treatment, be it

nociceptive pain or be it lower back or any other condition.

Q. So in fact it says that right in the label, correct?

A. Correct, yes.

Q. So if we can get up, Mr. Haw, again 1383, PTX 1383 and if we can just highlight the indications.

So again we have the first and the second indication severe and DPN and severe says the first indication is pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Correct?

A. That's correct.

Q. So that's consistent with what you just said about this type of product not being a first line option?

A. Yes.

Q. And then the second indication reads, neuropathic pain associated with DPN in adults severe enough to require daily around-the-clock long term opioid treatment and for which alternative treatment options are inadequate, correct?

A. Yes.

Q. Again, so it's not a first line option for those kinds of conditions, correct?

A. That's correct, yeah.

MR.FITZPATRICK: Thank you. No further questions.

THE COURT: Thank you.

Who do we have up next? Anyone? Mr. Schuler.

CROSS EXAMINATION BY MR. SCHULER:

THE COURT: It looks like we have additional exhibits.

MR. SCHULER: I may or may not.

THE COURT: Okay.

MR.FITZPATRICK: Do I get a prize for having the least number of exhibits?

(Laughter).

Q. Good morning, Dr. Haeussler?

A. Good morning.

Q. I'm sorry, good afternoon, Dr. Haeussler.

Is it fair to say that part of the analysis that Janssen had to undertake with regard to the DPN two pursuit was to determine the potential incremental revenue of having that additional indication?

A. I would assume so, even though I'm not on the commercial side.

Q. Do you recall being advised by your colleagues as to the magnitude of that potential additional revenue?

A. Not specifically, no.

Q. Let's see if I can refresh your memory here.

THE COURT: Let me just ask Counsel, any issue with this exhibit?

MR. KOTE: No, your Honor.

THE COURT: No?

MR. KOTE: No.

THE COURT: Thank you.

Q. Do you see, Dr. Haeussler, that you are listed both as a recipient on the earlier e-mail and as the sender of the later e-mail?

A. Yes.

Q. And if you see your colleague sent you an e-mail on January 29, 2009 commenting in the first part about whether there would be competition for enrollment of DPN patients. Do you see that?

A. Yes.

Q. And then in the third paragraph of her e-mail she says she also got some information from the commercial people about the added value of the DPN indication.

Doctor, do you see the third paragraph is talking about the commercial potential value?

A. Yes.

Q. Okay. And just do you see the Number $458 million?

A. Yes, I see the number, yes.

Q. And that's attributed to being the incremental cumulative value for the DPN indication over the lifetime of the product. Do you see that?

A. That's what is stated here.

Q. Does this refresh your memory as to the rough magnitude

of the estimates by Janssen as to the potential value of that added indication?

A. The problem is that this is one of many statements I have seen. I have seen estimates for the entire go from 200 million to 2 billion. And I have seen estimates for the incremental DPN indication going almost spanning another magnitude. So I don't recall which specific estimate I saw when.

Q. Fair enough. Is it fair to say that there was a consensus of the documents you saw or the numbers you were given that there was some added incremental value for DPN?

A. I would think so, yeah.

Q. Can you tell the Court your understanding as to how the addition of the DPN indication could expand the sales of Nucynta ER?

MR. KOTE: Objection to foundation.

THE COURT: Rephrase that question, please.

Q. Do you have an understanding --

THE COURT: Based on what? Why don't you ask based on whatever it is in his line of work.

Q. Based on your experience as an employee and head of the clinical trials, what was your understanding as to why the addition of the DPN indication would expand the potential sales for Nucynta ER?

A. I've heard many different potential explanations. But

the most important or the one that stuck in my mind most was the fact that it could be used specifically in a situation where the sales rep has a few seconds to talk to the doctor and doesn't have time to review a 40-page document.

Q. Okay. Now, I loved your joke on cross-examination, you said not only was it extensive, it was expensive.

Do you recall that?

A. Yes.

Q. Okay. How expensive was it to conduct the second DPN indication study?

A. I don't have a specific, I don't remember the specific numbers. But, all these studies range in the order of about $50 million.

Q. Did you say fifty million?

A. Yeah, five zero.

Q. Is it fair to say that at the time Johnson & Johnson was a public company, correct?

A. Yes.

Q. You were one of the upper management employees at the time?

A. Well, for R & D, not for any financial decisions.

Q. Understood. You understood that your company wasn't in the business of wasting shareholders' money, correct?

A. I hope not. I am a shareholder too.

Q. Fair enough. And so clearly Janssen determined that

there was some rational economic benefit to spending $50 million or so on that second study, correct?

A. Yes.

Q. And it's fair to say that the reason that Janssen thought that it was worth spending that money was to expand the patient population that Nucynta ER could be administered to, correct?

A. That sounds reasonable.

Q. Now, during your direct examination you spoke about the studies that were submitted to the FDA but you didn't discuss any of the documents where the FDA gave you feedback, correct?

A. Well, the ultimate feedback is the label.

Q. Fair enough. There's also FDA evaluations of the clinical studies, correct?

A. Yes.

Q. What's that called?

A. It's the -- are you referring to the summary basis of approval?

Q. Is there more than one FDA document where they review the clinical study?

A. I am sorry, I don't understand. You mean documents that are public or not public? Documents that are internal to FDA?

Q. Fair enough. We will backup a second. The FDA is a public agency?

A. Yes.
Q. They ultimately explain to the public their rationale for approval of a drug, correct?
A. Yes.
Q. And they did so with regard to Nucynta ER, correct?
A. Yes, it's the label.
Q. And they also publish what they call a clinical review, correct?
A. Yes.
Q. Do you recall how the FDA characterized the studies and study populations in the DPN one and LB, I'm sorry, lower back pain studies that you talked about?
A. No, I don't.
Q. Let's look at that together.
MR. SCHULER: Your Honor may I approach the witness and the bench?
THE COURT: Go ahead.
MR. SCHULER: I have marked it for identification as DTX 2007.
Q. If you turn to Page 2, do you see that this is the NDA review for Tapentadol hydrochloride ER?
A. It says clinical review.
Q. For Tapentadol extended release, right?
A. NDA 2053, yes.
Q. Okay. Now if you would turn with me doctor to the

page at the bottom there. It bears the Number 6. And this is the recommendations by the FDA with regard to Nucynta ER, correct?

MR. KOTE: Your Honor, before we get into this, I would like to have a foundation first.

THE COURT: I'm sorry, we didn't go through the documents?

Q. Sure. You reviewed this in the course of your work, sir?

THE COURT: Before we do that, you have looked at the document?

MR. KOTE: Yes.

THE COURT: Other than the foundation, do you have any issue?

MR. KOTE: No.

Q. Doctor, it was your responsibility to review this when it came into Janssen, wasn't it?

A. Yeah. It looks like but I really don't recall having reviewed this document.

Q. You testified on direct about all the feedback you got from the FDA and how it informed your personal view of the label. Do you recall that?

A. Yes.

Q. And this is part of that feedback, is it not?

A. Yes.

Q. All right. Let's look at efficacy. You understand what that is, correct?
A. Yes.
Q. All right. And it talks about in the third line the efficacy of Tapentadol ER in the treatment of chronic pain. You see that?
A. Yes.
Q. That was the original indication that you saw, right?
A. Yes.
Q. And it says it was established from two positive, adequate and well controlled trials. Do you see that?
A. Yes.
Q. I think you were the one that said on direct there were only two studies that the FDA regarded as meeting that positivity criteria, right?
A. That's what we were told, yes.
Q. And the first one is study number 11. Do you see that?
A. Yes.
Q. Was that a lower back pain study?
A. Yes.
Q. And study 15 was the DPN one study, correct?
A. Yes.
Q. Then it says with supportive evidence from study eight. And if we go to the next sentence it says the two positive trials had different designs i.e induction and an enriched

randomized withdrawal design, right?

A. Yes.

Q. And then they had different populations, right?

A. Yes.

Q. Low back pain and painful diabetic peripheral neuropathy, correct?

A. Yes.

Q. And different types of pain, correct?

A. Yes.

Q. Nociceptive and neuropathic, correct?

A. Yes.

Q. Thereby providing heterogenous designs and populations for study of Tapentadol ER, correct?

A. Yes.

Q. This is the FDA's characterization of those studies, is it not?

A. Yes.

Q. So there's no question, I would like you to turn to one other page or two other pages, the review of Dr. Brodski. It's about two-thirds of the way through. And we will put it on the screen for you. And we'll start at Page 4 of 129. And if we could go to the third paragraph Results.

And, again, do you see the reference to the two trials 11 and 15?

A. Yes.

Q. Okay. And let's turn two pages forward to Page 6 of 129 in summary.

And Dr. Brodski says In summary, the efficacy of Tapentadol ER in the chronic treatment of pain was established from two positive, adequate and well controlled trial studies 11 and 15.

Do you see that?

A. Yes.

Q. And then he says, the next sentence, the heterogenous designs/populations of the two positive trials supports the efficacy of Tapentadol. The two positive trials had different designs, different populations and different types of pain (nociceptive and neuropathic pain).

Do you see that?

A. Yes.

Q. And that's characterization of the FDA's medical doctor that reviewed these clinical studies, correct?

A. It seems so, yeah.

MR. SCHULER: No further questions.

THE COURT: Thank you.

Counsel.

MR. ALY: Yes.

THE COURT: Exchange any documents, exhibits you may be using, please.

MR. ALY: Yes, your Honor. I have given up on

binders so I have two paper clips.

THE COURT: That's good. It's getting less and less.

MR. ALY: May I approach?

THE COURT: Yes, please do.

MR. KOTE: As long as there is a foundation, I have no objection

CROSS EXAMINATION BY MR. ALY:

Q. Hi, Dr. Haeussler.

A. Hello.

Q. I would like to talk with you about two document, first DTX 1366 please. This is a document titled Safety and efficacy of Tapentadol ER in patients with painful diabetic peripheral neuropathy, DPN, correct?

A. Yes.

Q. And it's comparing Tapentadol to placebos, correct?

A. Yes.

Q. It's not comparing Tapentadol to Tramadol, correct?

A. Yes.

Q. And you're an author on this particular paper, right?

A. Yes.

Q. On the next page, Page 2, there's an introduction and there's a sentence that refers to how pure MU opioid analgesics have demonstrated some positive effects but they are not considered adequate with regard to tolerability.

Do you see that?

A. Yes.

Q. That's in your paper, right?

A. Yes.

Q. And for the citations you have these documents numbered 4 through 10, correct?

A. Yes.

Q. I would like to look at the last page of the document, Page 12, where those citations can be found. Looking at citation Number 10, that reference is to the Harati article from 1998, correct?

A. Yes.

Q. And the title of that article is Double-blind randomized trial of Tramadol for the treatment of the pain of DPN, correct?

A. Yes.

Q. And so when you're referring in your article to something that says there are other options but they are not very good at addressing side effects, one example you refer to is the Harati article, right?

A. Yes.

Q. Let's look at the Harati article, DTX 1605 Page 2. And so first let's confirm this is the Harati article that you cited, correct?

A. Yes.

Q. From the cover page let's go to Page 2 of the document, this section here where we talk about the introduction and background. And there is a discussion of the problem but also the solution.

Do you see here, sir, Dr. Haeussler, that the treatment of neuropathic pain in diabetes as well as other small fiber neuropathies such as idiopathic sensory or HIV associated neuropathy is often difficult and unsatisfactory. You see that, right?

A. Yes.

Q. Then the next sentence says, Given the limitations of the available therapies, new compounds that are effective and well tolerated need to be identified for pain management in patients with diabetic neuropathy, right?

A. Yes.

Q. In fact, it goes on to suggest Tramadol as that solution to the problem, correct?

A. At that time, yes.

Q. Let's go to Page 6, please, this coupled with this.

Please, Mr. Haw, the lower left paragraph and it concludes on the top right.

Now, the Harati article concludes, does it not, Dr. Haeussler, that the outcome of the placebo-controlled trial indicates that the Tramadol is an alternative to other drugs where they don't work, specifically for DPN, right?

A. Yes.

Q. And it goes on to say that one benefit is there is the low incidence of anticholinergic side effects and somnolence with Tramadol, right?

A. Yes.

Q. Showing that it is better tolerated than other alternative drugs that are available, correct?

A. Its refers to non opioid, two different classes.

Q. And in the work that you suggested on direct examination, all of the Tapentadol clinical trials that you've done at Janssen or that you are aware of, you have never compared Tapentadol on the one hand to Tramadol on the other. Isn't that true?

A. I don't recall any direct comparison.

Q. That would have been called a head-to-head comparison, correct?

A. Yes.

Q. And Ultram is something that Janssen still sells today, right?

A. Yes.

Q. And that's Tramadol, correct?

A. Yes.

MR. ALY: That's all.

THE COURT: I think we are done with you on the defendants' side with cross. Any redirect?

MR. KOTE: Just a few questions, your Honor.

THE COURT: Yes, go right ahead.

REDIRECT EXAMINATION BY MR. KOTE:

Q. Dr. Haeussler, on your cross you were asked about some exclusions that were made with respect to the DPN two study.

Would those same exclusions have been made in the DPN one study?

A. Yes. As I mentioned, these are like very standardized criteria that we are always using.

Q. You were also asked some questions on cross regarding promotion of Nucynta.

Do you recall that?

A. Yes.

Q. Are you aware of any prohibitions from a salesperson, for example, to talk about the clinical trials that are used to support an indication that are listed in the label?

A. No, other than time.

Q. If the FDA had rejected the DPN one study that was relied upon to get the original indication for moderate-to-severe chronic pain, would Janssen have received the approval for Nucynta ER originally?

A. Well, all I can say is based on the guidance that we received at the specific meeting, and there was the specific statement from FDA that we required two positive studies by their standards, and these are the only two positive studies by

their standards that they told us, so, I can only infer that if one of the two studies would not be considered or not been included, that there would have been no approval.

MR. KOTE: No further questions.

THE COURT: Thank you.

Are we done?

MR.FITZPATRICK: Yes, your Honor.

THE COURT: Yes. All right. We are done with this witness. Thank you so much for coming in, sir. Much appreciated. You may step down from the stand. Your testimony is complete. Thank you so much. You are released.

I believe at this point we are ready for our lunch break. It's 10 to 1 so we will have 45 minutes, or do you want to shave it back to 30 minutes? I don't know how you stand with your witnesses.

MR.FITZPATRICK: Thirty minutes would be preferred.

THE COURT: Is 30 minutes preferred by everyone? Your food has arrived so you should be fine with 30 minutes. We will see you then in 30 minutes. Thank you.

(Lunch recess).

THE COURT: Let's get an estimate on the afternoon so we can all be on the same page as to the schedule. Just roughly.

MR. CAPUANO: We will have Dr. Michael Weinberger

who we anticipate on the direct exam will be right around an hour.

THE COURT: That sounds good. Do we know what we are going to get in response, roughly ?

MR. CAPUANO: A few minutes, I imagine. Nothing more.

(Laughter).

MR. CHUNG: About 30 minutes.

THE COURT: Obviously I'm not going to hold anyone to anything. I'm trying to figure out do we have enough time to do our witnesses. Sounds fine.

MR. CAPUANO: Dr. Mogil will testify approximately an hour 15 minutes or so.

THE COURT: Thoughts on cross.

MR. SITZMAN: Probably 45.

THE COURT: We should be able to do everything. Sounds good. Okay. So now we are going out of order. Is that it?

MR. CAPUANO: We are going to go out of order due to some schedule concerns.

THE COURT: He's coming from Actavis. Is that it?

MR. CAPUANO: Yes, ma'am.

THE COURT: All right. There's no objection? I know we discussed this in advance. Obviously there's no

objection to going out of order, correct?

MR. CAPUANO: It's all been worked out.

MR. CHUNG: No, your Honor.

THE COURT: Thank you. Let's begin. You can call the witness.

MR. CAPUANO: Your Honor, Actavis calls Dr. Michael L. Weinberger, M.D.

I have some exhibit books to hand out.

THE COURT: Are you good with the exhibits? Have you taken look?

MR. CHUNG: Yes, your Honor.

THE COURT: Thank you.

M I C H A E L L W E I N B E R G E R, sworn and testifies as follows:

DIRECT EXAMINATION BY MR. CAPUANO:

THE COURT: You may begin.

Q. Good afternoon, Dr. Weinberger.

A. Good afternoon, sir.

Q. For the record, would you please state your name?

A. Michael L. Weinberger.

Q. Where do you live, Dr. Weinberger?

A. New York.

Q. And have you prepared a set of demonstrative exhibits to help you explain your background and opinions to the Court?

A. Yes, sir.

Q. If I could just have the next slide.

Dr. Weinberger, please describe briefly for the Court your educational background including the degrees that you hold.

A. Sure. I got a B.A. from Clark university, M.D. from Columbia university college of physicians and Surgeons. I trained in internal medicine in St. Vincent's hospital in New York. I trained in anesthesiology at Columbia university. I did a fellowship in pain medicine at Sloan Kettering. And I'm currently board certified in anesthesiology, internal medicine pain medicine and hospice and palliative medicine.

Q. Do you have currently any medical specialties?

A. My specialty is pain medicine.

Q. Okay. How long have you been working as a pain management specialist?

A. About 26 years or so.

Q. You are currently at Columbia. Is that correct?

A. Yes, sir.

Q. What is your current position at Columbia?

A. I am an associate clinical Professor at the university. I am the director of the pain management center. And I'm the section chief of the division of pain medicine within the division of anesthesiology at the university and at the medical center.

Q. What are your duties with respect to those various

positions?

A. The majority of my duties are practicing clinical medicine. But I also have administrative duties as the section chief of chief residents and fellows and medical students and do a little bit of research.

Q. Do you split your time between time in the clinic and time at the hospital?

A. Basically I spend about 80 percent of my time in the office which is off campus and 20 percent of my time at the hospital.

Q. How much of your time is spent evaluating your patients and their pain?

A. Probably about 95 percent or so.

Q. Okay. And in your field of pain management, how do you and other physicians evaluate a patient to determine the severity and nature of their pain? And have you put together a slide to help you explain that?

A. Yes, sir. The practice of pain medicine is /S similar to the practice of medicine in general. We see patients. We do a complete history. We do a physical exam. And we then look at the appropriate studies that may be relevant to whatever the patient's condition is.

In the field of pain medicine, there may be specific things that we ask related to pain, severity of pain using pain scores and things like that. But, the practice of pain

medicine is not that much different than the practice of medicine in general.

Q. In your practice do you see patients who are suffering from severe pain?

A. Yes, sir.

Q. And do you see patients who are suffering from polyneuropathic pain?

A. Yes, sir.

Q. And on this slide have you summarized what goes into making a diagnosis of polyneuropathic pain? And doctor it's on the screen and it's also in our book.

A. Well, this is some of the things that we look for when trying to evaluate whether a patient has neuropathic pain. Again we take a history. We will do a physical exam. We look for signs that may be consistent with abnormalities of the nervous system.

We may look at appropriate imaging studies or other diagnostic studies. And sometimes you will see the use of a pain detect questionnaire which is also designed to basically look for qualities of pain that are consistent with neuropathic pain.

Q. Could I have defendant's Exhibit 1663, please?

It's up on your screen too, doctor, if that's easier.

A. Thank you.

Q. You mentioned the pain detect questionnaire.

A. Yes, sir.
Q. And do you recognize defendant's Exhibit 1663?
A. Yes, sir.
Q. What is defendant's Exhibit 1663?
A. This is the pain detect questionnaire which I see most commonly used for studies where they are trying to look at groups of patients and determine which patients may have neuropathic pain.

So there are questions on here that would lead one, might be consistent, if the person answers positively then it may lead to the possibility that the patients has a neuropathic pain condition.

Q. Can we just blow up this area here?

And how does this questionnaire and these questions in particular give a pain specialist information that can distinguish between somebody suffering from polyneuropathic pain and some other form of pain?

A. Well, we often talk about different types of pain being qualitatively different. And neuropathic pain is often described as being shooting or lancinating. It may be burning in sensation .

Patients with nerve involvement may have other associative phenomenon, numbness and tingling, paresthesias. They may have other associated nerve related phenomenon that patients with nociceptive pain may not. So, this is a tool

that's used to try to determine whether there might be likelihood that these patients have neuropathic pain.

Q. Are the questions on this questionnaire similar to the questions that you would ask a patient during a patient's history evaluation.

A. Absolutely. And they are similar to the list of questions that were on the slide previous to this.

Q. Dr. Weinberger, are you aware if there are any accepted definitions for polyneuropathic pain and nociceptive pain?

A. Well, I prepared a slide to basically differentiate nociceptive pain and polyneuropathic. These are not my definitions, these are definitions from the International association for the study of pain. They are an international organization that basically is a leader in research and education.

And because many of the terminology that we use for describing pain and pain symptoms are different than in general medicine, they basically developed a taxonomy where these terms are defined.

Q. Could you pull up defendant's Exhibit 1667, please ? And could you split pages 4 and 5 and then maybe zoom in on the neuropathic pain on the left and nociceptive pain on the right?

Dr. Weinberger, what is the IASP definition for nociceptive pain?

A. So, they define nociceptive pain as pain that arises

from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

So it's not nerve tissue and again potential for real tissue damage creating pain.

Q. Okay. And what are some examples of when somebody might feel nociceptive pain?

A. Okay. A broken bone would be an example of nociceptive pain. An example of threatened tissue damage may be someone gives you a hug it doesn't hurt, squeezes you, and you have the potential that that continues causing tissue damage, that would be another example in a sense.

Q. You said part of that is a protective mechanism. You drop a hot pot.

A. So your tissues don't get hurt. That is another example of nociceptive pain.

Q. On the other page that we were looking at, defendant's Exhibit 1667, what east the IASP definition for polyneuropathic pain or, sorry, neuropathic pain?

A. Pain caused by a lesion or disease of the somatosensory nervous system.

Q. And what are some conditions that would cause polyneuropathic or neuropathic pain?

A. Post traumatic neuralgia, herpes zoster, shingles, chemotherapy-related pain, idiopathic neuralgia, lots of conditions.

Q. And is there a way for you to explain the difference between nociceptive pain and polyneuropathic pain other than through the definitions?

A. Again, the symptoms tend to be different and the mechanism is different. The mechanism of nociceptive is tissues other than neural. And for neuropathic pain, there's lesions within the sensory, within the nervous system.

Q. Is it the case that nociceptive pain can be severe and chronic?

A. Yes, sir.

Q. And is it also the case that polyneuropathic pain can be severe and chronic?

A. Yes, sir.

Q. Is it also the case that some pain is both polyneuropathic and nociceptive?

A. Yes, sir, can be.

Q. Is it the case that in the population of people with severe pain that a subpopulation of that group is suffering from polyneuropathic pain?

A. I would guess that is true.

Q. Are there different lines of treatment for polyneuropathic pain? And have you made a slide to help you explain that?

A. Yes, sir.

Q. Let's turn to that slide. What do you have here on

this slide?

A. Well, neuropathic pain is often considered difficult to treat. And often when you're choosing medications, many of these medication are only effective in less than 50 percent of the time for treatment of neuropathic pain. So, we talk about first line, second line, third line treatment.

First line treatments tend to be antidepressants and anticonvulsants. The classic antidepressants tend to be effective for neuropathic pain and tricyclic antidepressants or other antidepressants like selective serotonin neuropathy reinhibitors and neuro reuptake inhibitors.

And the anticonvulsants such as gabapentin and pregabalin can be effective or different anti-convulsants, different classic drugs can be effective for the treatment of neuropathic pain.

There is also a mistake on the slide, amitriptyline and duloxetine are antidepressants.

THE COURT: The first and the last on that list on the line?

THE WITNESS: Yes, ma'am.

Q. Let's have defendant's Exhibit 1665, please.

Dr. Weinberger, have you reviewed what is defendant's Exhibit 1665?

A. I have, sir.

Q. And what is defendant's Exhibit 1665?

A. This is a consensus statement from the Canadian pain society and recommendations on the pharmacological management of chronic neuropathic pain.

Q. And if we look at the abstract there is a subsection of the abstract called Results. Do you see it's right in here.

A. Yes, sir.

Q. If you could just read into the record the first two sentences of the results section?

A. Analgesic agents recommended for first line treatments are gabapentinoids, in parenthesis gabapentin pregabalin, tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors.

Tramadol and controlled-released opioid analgesics are recommended as second line treatments for moderate to severe pain.

Q. If you can split exhibit pages 2 and 3, at the bottom of Page 2 of the exhibit starts a heading First line analgesics.

Do you see that Dr. Weinberger?

A. Yes, sir.

Q. Okay. And then that continues on to the next page. And what's being described here in this paper, doctor?

A. This section is description of the first line analgesics. And there are two classifications that they consider first line, anticonvulsants and certain

antidepressants.

Q. And just below this if you can see the antidepressant section, is this a description of antidepressant agents that are considered first line treatment for neuropathic pain?

A. Yes, sir.

Q. And at the bottom of that same column on Page 3 of the exhibit 1665, defendant's Exhibit 1665, there is a section called Second line analgesics.

Do you see that?

A. Yes, sir.

Q. And what's the first second line analgesic that is mentioned there?

A. Tramadol.

Q. Okay. And on the next column that continues you will see over on the right hand column, this section up here, do you see that section that says opioid analgesics?

A. Yes, sir.

Q. And would you include Tapentadol as an opioid analgesic as a second line treatment for neuropathic pain?

A. Tapentadol is considered an opioid so, yes, I would consider it a second line agent for treatment.

Q. Let's look at defendant's Exhibit 1666 please, Dr. Weinberger.

Have you reviewed what's been labeled as defendant's Exhibit 1666?

A. Yes, sir.

Q. What is defendant's Exhibit 1666?

A. It is a review by O'Connor and Dworkin of treatment recommendations or recent guidelines for the treatment of neuropathic pain. And in this study they actually looked at I think it was four different sets of guidelines by different organizations and reviewed them.

Q. And if we can just turn to Table 4 in this document, it's on exhibit Page 9 at the top.

Do you see Table 4 in Exhibit 1666, Dr. Weinberger?

A. Yes, sir.

Q. What's being described in Table 4?

A. I may have misspoke. This is basically the medication classes are on the left and on the right they list the guidelines from the three separate organizations and how those medications were arranged.

Q. And is the description of first and second line treatments for polyneuropathic pain in the papers we looked at defendant's Exhibit 1665 and 1666 consistent with your experience and your understanding of how other physicians treat neuropathic and polyneuropathic pain?

A. It is, sir.

Q. Okay. And in your practice you see patients and diagnose them as having polyneuropathic pain. Is that right?

A. Yes, sir.

Q. And for those patients you see who are suffering from polyneuropathic pain, how do you make prescription decisions for those patients?

A. That's a somewhat complex answer. There are a variety of factors that go into making that decision. We look at a patient's history, their associative medical conditions, if they have allergies to medication. Often the patients I see are more complex and have had been prescribed other medications, so I need to take into fact what other medications they've had.

And I need know any of the side effects of the medications that I might be prescribing and then use the best available evidence on what I think might be effective.

Again for neuropathic pain that can be difficult because often in the best of hands probably we get 60 percent efficacy in a group of patients. So maybe 1.6 out of, we need to treat 1.6 patients to get efficacy. But the efficacy is pretty much not that good.

Q. Have you described antidepressants and anticonvulsants for treating polyneuropathic pain in your patients?

A. Yes.

Q. Which antidepressant and anticonvulsants have you prescribed?

A. I think I used all of them. Again, certain antidepressants are effective for neuropathic pain. So drugs

like amitriptyline, duloxetine, neuritin are drugs are examples of antidepressants. I've used gabapentin and other anticonvulsants as well. The list is long.

Q. And Dr. Weinberger, have you prescribed opioids as a second line treatment for neuropathic and polyneuropathic pain?

A. Yes, sir.

Q. Which ones have you prescribed?

A. Over a handful of opioids that we have available to us and examples would be codeine, morphine, Methadone, hydromorphone. So all of those and others Fentanyl, all of those and others I have probably used on occasion for the treatment of neuropathic pain.

Q. Have you prescribed Tramadol for treating neuropathic and polyneuropathic pain for your patients?

A. Yes, I have.

Q. And have you prescribed Tapentadol Nucynta ER for treating neuropathic and polyneuropathic pain for your patients?

A. I believe I have.

Q. Among the patients that you prescribed an opioid or second line treatment for neuropathic pain, do you have any idea what percentage is being prescribed Tapentadol?

A. I would imagine less than ten percent.

Q. Dr. Weinberger, have you ever testified at trial in the U.S. before?

A. Yes, sir.

Q. In those cases where you've testified at trial, were you acting as an expert in pain management?

A. Yes, sir.

Q. And in any of those cases are you aware of any Court that did not accept you as an expert in the treatment of pain?

A. No, sir.

MR. CAPUANO: Your Honor, Actavis offers Dr. Weinberger, M.D., as an expert in diagnosis and management of pain, including severe and polyneuropathic pain.

THE COURT: Thank you.

Any issue with that?

MR. CHUNG: No, your Honor.

THE COURT: All right. He is so deemed as an expert. Thank you. You may proceed.

MR. CAPUANO: Thank you, your Honor.

Q. Dr. Weinberger, do you understand in this case that plaintiffs have alleged that Actavis will induce infringement and contribute to infringement of what's been referred to as the '130 patent?

A. Yes, sir.

MR. CAPUANO: Your Honor, I am coming up to soon the point where we will need to clear the courtroom of anybody who is not under the protective order.

THE COURT: Do you want me to do that or you are

getting there, what, in a couple of minutes? Ten minutes?

MR. CAPUANO: Three pages.

THE COURT: When you are ready, just let me know.

MR. CAPUANO: Okay. Thanks.

Q. Dr. Weinberger, have you reviewed the '130 patent?

A. Yes, sir.

Q. And if you could just blow up the title here, Ted.

What's the title of the '130 patent, Dr. Weinberger?

A. Use of 1-phenyl-3-dimethylaminopropane compounds for treating neuropathic pain.

Q. And could I have Dr. Weinberger's next slide, please?

Dr. Weinberger, based on your review of the '130 patent, what would you say is the object of the alleged invention of the '130 patent?

A. Production of medication or predicament for treating neuropathic pain, preferably polyneuropathic pain.

Q. Okay. Does the specification of the '130 patent describe the invention as the treatment of all kinds of pain?

A. It's specific for neuropathic pain and polyneuropathic pain.

Q. Does the '130 patent describe the invention as the treatment of nociceptive pain?

A. No, sir.

Q. Does the '130 patent describe the treatment of visceral pain.

A. No, sir.
Q. Just for the Court, what is visceral pain?
A. Visceral pain is pain from an organ. An easy way to understand it might be pain you get when you have a gallbladder attack or the pain of pancreatic cancer.
Q. Does the '130 patent describe that the invention is the treatment of all forms of severe pain?
A. No, sir.
Q. And Dr. Weinberger, have you had a chance to review the Patent Office prosecution history for the '130 patent?
A. I have, sir.
Q. Do you have a slide summarizing that history?
A. Yes, sir.
Q. The next slide please.
Based on your review of the Patent office file history for the '130 patent, the patent examiner initially rejected Grunenthal's claims based upon the original Grunenthal patent to Dr. Buschmann?
A. That is my understanding, sir.
Q. And what did the Patent Office examiner say in his rejection when he rejected Grunenthal's claims over Dr. Buschmann's original Tapentadol claim?
A. Basically said that Buschmann teaches that substances with an analgesic effect which are suitable of the treatment of severe pain without giving rise to the side effects which are

typical of opioids and that of tramadol. Treatment of pain taught by Buschmann is inclusive of the neuropathic pain such as polyneuropathic pain.

Q. Did the patent examiner point out that Dr. Buschmann's original patent described the use of Tapentadol for the treatment of severe pain?

A. Yes, sir.

Q. And did the patent examiner point out that the treatment of severe pain taught by Dr. Buschmann included the use to treat polyneuropathic pain?

A. Yes, sir.

Q. And can we have the next slide ?

And did you review how Grunenthal responded to this rejection?

A. Yes, sir. They basically said that Buschmann does not disclose or suggest that its compounds are useful for treating polyneuropathic pain or polyneuropathy.

Q. Does this response by Grunenthal give you any information about whether Grunenthal believed that the description of treating severe pain in Buschmann's patent could be viewed as a specific description of using Tapentadol to treat polyneuropathic pain?

A. I think they felt that it was not included in the original Buschmann description and therefore was worthy of a new patent.

Q. Let's look at the next slide please.

Dr. Weinberger, do you understand that Actavis has been accused of inducing infringement and contributing to infringement of claims 1 and 2 of the '130 patent?

A. That's my understanding, sir.

Q. And you have those two claims here on this slide?

A. Yes, sir.

Q. And just for the record, and you can for the chemical name just shorten it to Tapentadol, but could you read into the record claims 1 and 2 of the '130 patent?

A. Claim one is A method of treating polyneuropathic pain in a subject suffering therefrom, said method comprising administering to said subject an effective polyneuropathic pain inhibiting amount of path Tapentadol or a pharmaceutically acceptable salt thereof.

Claim two, a method according to claim one, comprising administering a hydrochloride salt of Tapentadol.

Q. Dr. Weinberger, based on your review of the patent and its patent office file history and the granted claims, what type of pain do you consider to be the subject of the claims that have been asserted against Actavis?

A. Neuropathic pain, specifically polyneuropathic pain.

Q. And in your opinion could the asserted claims against Actavis be reasonably understood to be directed to the treatment of severe pain generally?

A. No, it's specific for neuropathic or polyneuropathic pain.

MR. CAPUANO: I am now at the point where we are going to start talking about confidential information, your Honor.

THE COURT: All right. So we are going to seal the courtroom at this point. Let us have those who are not the clients here, anyone else on the outside world, exit the courtroom at this point. Obviously trial teams are permitted to stay in the room. So we will just take a little tally as soon as the courtroom clears.

Let's just make sure. I'm going to do it the same way we did it before. We will do it really fast. Whose here for Grunenthal, Depomed, Actavis, Roxane, Alkem? Anyone who is not seated, counsel, you recognize your people. All right. We're all fine. Yes.

Let's proceed. The courtroom is sealed. Go ahead.

MR. CAPUANO: Thank you, your Honor.

THE COURT: The transcript here is sealed too.

MR. CAPUANO: Thank you, your Honor.

THE COURT: Thank you.

(Whereupon the hearing is under seal)*.

(Whereupon the matter was concluded)